In the United States Court of Federal Claims
OFFICE OF SPECIAL MASTERS

ANGELICA VINESAR and MARIUS VINESAR as best friends of their daughter, A.V.,	*	No. 18-440V
	*	Special Master Christian J. Moran
Petitioners,	*	
	*	Filed: July 28, 2023
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

John F. McHugh, New York, NY, for petitioners;
Julia M. Collison, United States Dep't of Justice, Washington, DC, for respondent.

DECISION DENYING ENTITLEMENT TO COMPENSATION[1]

Mr. and Ms. Vinesar allege that various vaccinations caused their daughter (A.V.) to suffer a seizure disorder. Pet., filed March 23, 2018. The parties have developed evidence, particularly opinions from experts on this topic as well as the issue as to whether a genetic variant in A.V.'s SCN1A gene caused the seizure

[1] Because this Decision contains a reasoned explanation for the action taken in this case, it must be made publicly accessible and will be posted on the United States Court of Federal Claims' website, and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc, in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). This means the Decision will be available to anyone with access to the internet. In accordance with Vaccine Rule 18(b), the parties have 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. Any changes will appear in the document posted on the website.

disorder independently. The parties also submitted briefs and participated in an oral argument.

The evidence is similar to the evidence in other cases in which special masters have found that an SCN1A mutation solely caused a child's seizures. The outcomes and findings of facts, as extensively discussed below, have been affirmed by the Court of Federal Claims and the Federal Circuit. Although the Vinesars argue that a 2020 opinion from the Federal Circuit has altered the legal landscape, the Vinesars's argument fails to account for other precedents from the Federal Circuit. Due to the prominence of the Vinesars's legal arguments, the series of cases that provide a background to SCN1A litigation are set forth in Section I as an introduction.

The outcomes of those cases, however, do not preclude the Vinesars from receiving compensation if the evidence differed. Thus, the evidence regarding the events in their child's life are detailed in Section II. Those events are the foundations for the Vinesars's claim that typical childhood vaccinations harmed their daughter, and the procedural history is briefly outlined in Section III. The standards for adjudication are presented in Section IV.

The analysis is found in two parts. Section V considers whether a vaccination caused A.V.'s seizure disorder. Section VI addresses whether the genetic mutation by itself caused A.V.'s seizure disorder. As explained in Section VII, a hearing is not required to resolve these questions in part because numerous other cases have considered very similar issues.

I. Precedents Involving Children with Genetic Variants

Within the last thirteen years, the Federal Circuit has reviewed eight decisions by special masters in cases in which a child with a genetic variant received a vaccine and developed problems.[2] Many of the decisions from special masters are lengthy, reflecting the complexity of the issues. Thus, the special masters' decisions are summarized extensively below. The special masters' decisions are the foundations for actions taken by the Federal Circuit, which constitute binding precedent. The Federal Circuit's rulings must be read in context. See Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc., 769 F.3d 1339, 1353 n.1 (Fed. Cir. 2014) (Taranto, J., dissenting from denial of a petition for rehearing *en banc*) ("It is a well-recognized principle, and one essential

[2] An appendix is provided for cases with a lengthy history.

to our system of precedent, that statements in opinions must be read in context, considering their role in the decision and the facts of the case").

A. Stone/Hammitt

Although Stone and Hammitt were consolidated at the Federal Circuit, the chief special master separately adjudicated them initially. Thus, they are summarized one at a time.

1. Stone

The daughter of Jennifer and Gary Stone, Amelia, received a dose of the diphtheria-tetanus-acellular pertussis ("DTaP") vaccine as part of her four-month well-child pediatric appointment. Stone v. Sec'y of Health & Hum. Servs., No. 04-1041V, 2010 WL 1848220, at *2 (Fed. Cl. Spec. Mstr. Apr. 15, 2010), mot. for rev. granted, 95 Fed. Cl. 233 (2010). The day after her vaccination, Amelia experienced two seizures, each of which lasted about thirty minutes. Id. at *2. After being hospitalized, Amelia was found to have returned to her usual state of health and an MRI did not identify any abnormalities. Id.

Following approximately two years of periodic seizures, a pediatric neurologist diagnosed Amelia as suffering from Dravet syndrome. Id. at *3. More than one year later, a genetic test revealed that Amelia possessed a de novo mutation in her SCN1A gene. Id.

Mr. and Ms. Stone alleged that the DTaP vaccine caused Amelia to develop Dravet syndrome. Id. at *1. To assist with their claim, Mr. and Ms. Stone retained Dr. Marcel Kinsbourne. The essence of Dr. Kinsbourne's opinion was that "the pertussis vaccination caused the fever; that the fever caused a prolonged seizure classifiable as complex febrile, and indeed status epilepticus. That seizure caused harm to the children, and that harm was reflected in a lowering of level of seizure propensity, thus facilitating future seizures." Id. at *10 (citing Tr. 2 at 443).

To address the genetic issues, the Secretary retained Dr. Gerald Raymond. To start, Dr. Raymond recognized that "a vaccination can cause a fever; a fever can trigger a seizure, including a complex febrile seizure; and a complex febrile seizure can cause brain damage." Id. at *11. However, "Dr. Raymond opined that Amelia's vaccinations neither caused nor exacerbated her [Dravet syndrome], but rather a mutation in her SCN1A gene is solely responsible for her [Dravet syndrome]." Id. at *13. Dr. Raymond pointed to the following factors as significant to his opinion that the SCN1A gene caused Amelia's condition:

> Amelia's mutation arose de novo;
>
> the mutation at issue results in a non-conservative amino acid change with the new amino acid having very different physical properties from what is found at that location in non-affected individuals;
>
> the mutation affects the pore of a sodium channel, a functionally important region;
>
> the mutation occurs in an area that is well conserved across species, signaling significant ramifications when altered;
>
> there are reports evidencing similar or comparable mutations resulting in [Dravet syndrome]; and
>
> there is an absence of the mutation in the normal population.

Id. at *41.

The chief special master resolved the case in a decision, which exceeded thirty pages, noting that Stone's significance in the Vaccine Program is a rare example of a case in which the Secretary was contending that a factor unrelated to a vaccine (the SCN1A gene) caused the vaccinee's condition. Id. at *12-13. Commensurate with the case's importance, the chief special master described genes, protein synthesis, and the SCN1A gene specifically. Id. at *13-15.

Ultimately, the chief special master found that the Secretary had "demonstrated by a preponderance of the evidence that Amelia's SCN1A gene mutation was more likely than not the 'but for' and 'substantial factor' that caused her . . . Dravet Syndrome." Id. at *42. The chief special master provided several reasons for this finding including the disparity in the credentials between Dr. Kinsbourne, who "has no past or present experience or credentials in the field of genetics," and Dr. Raymond, who "provided a complete and thorough review of the underlying genetics in this matter and then applied the medical principles and his clinical experience as a geneticist and pediatric neurologist to the facts of this case." Id. at *40.

The chief special master also extensively reviewed the factors that Dr. Raymond considered in concluding that the SCN1A gene caused Amelia's Dravet

syndrome. Id. at *20-38 (see factors listed *supra*). In short, the decision found those factors to be an appropriate way for clinical geneticists to counsel their patients. The decision emphasized that no evidence showed that the initial seizure harmed Amelia. Accordingly, Mr. and Ms. Stone were denied compensation.

Mr. and Ms. Stone sought review of the April 15, 2010 decision. A judge from the Court of Federal Claims held that the chief special master "failed to apply the correct legal standard to respondent's evidence of a factor unrelated to the vaccine." Stone v. Sec'y of Health & Hum. Servs., 95 Fed. Cl. 233, 238 (2010) (noting that "[i]n order to enter judgment for respondent, the special master would have to have found that the SCN1A gene mutation was the 'sole cause' or 'principally responsible' for Amelia's SMEI"). The judge, thus, remanded the case.

Upon remand, the chief special master found "beyond any doubt that respondent proved by a preponderance of the evidence that Amelia's SCN1A gene mutation was the sole cause and was principally responsible for her [Dravet syndrome]." 2011 WL 836992, at *3 (Fed. Cl. Spec. Mstr. Jan. 20, 2011).

Mr. and Ms. Stone sought a second review by a judge of the Court of Federal Claims. This time, the judge denied the motion for review. 99 Fed. Cl. 187 (2011). Specifically, the judge ruled that a specific genotype-phenotype study was not required for Dr. Raymond to predict the outcome of the SCN1A mutation in Amelia. Id. at 190. The judge acknowledged Dr. Raymond's position as the only expert in genetics to testify. Id. at 190-91. The judge also found that the chief special master was not arbitrary in rejecting Dr. Kinsbourne's opinion that the vaccine-induced fever lowered Amelia's seizure threshold. Id. at 191. Finally, the judge found that the evidence supported the chief special master's finding that Amelia did not suffer any lasting brain damage from her two initial seizures. Id. at 191-92. Accordingly, the Court entered a judgment against Mr. and Mrs. Stone. Id. at 193.

2. Hammitt

Around the same time the chief special master was resolving Stone, the chief special master also was considering a similar case that Scott Hammitt brought on behalf of his daughter, Rachel.[3] No. 07-170V, 2010 WL 3735705 (Fed. Cl. Spec. Mstr. Aug. 31, 2010). Rachel received her second dose of the DTaP vaccine when

[3] After the remands from the Court of Federal Claims, the chief special master conducted a consolidated hearing to receive testimony from the experts.

she was four months old. That evening, Rachel experienced a seizure lasting approximately forty-five minutes for which she was given Valium. Id. at *2. A CT scan was normal and by the next day, Rachel was "playful and cheerful." Id.

Rachel had a second seizure about one month later and the CT scan was again within normal limits. However, an EEG showed "focal epilepsy." Id. Rachel experienced more seizures, and her development was recognized as delayed when she was 14 months old. Id.

A genetic test revealed that Rachel had a de novo mutation in her SCN1A gene. Id. at *3. She was diagnosed with severe myoclonic epilepsy of infancy ("SMEI"), which is also known as Dravet syndrome. Id. at *10.

Like Mr. and Ms. Stone, Mr. Hammitt retained Dr. Kinsbourne to explain how the vaccine harmed his daughter. Dr. Kinsbourne opined "that Rachel was predisposed to suffer seizures due to her SCN1A genetic mutation. However, Dr. Kinsbourne further opined that Rachel's DTaP vaccination was a substantial contributing cause of her seizure disorder in addition to her genetic predisposition." Id. at *10 (internal citations omitted).

The Secretary again predominantly relied upon an opinion from Dr. Raymond. Dr. Raymond maintained that "a mutation in [Rachel's] SCN1A gene is solely responsible for her [Dravet syndrome]." Id. at *16.

The analysis from the chief special master is essentially the same as the analysis in Stone. Id. at *23-45. As such, he found that Mr. Hammitt was not entitled to compensation. Id. at *47.

Mr. Hammitt filed a motion for review, and, although the opinion is not reported, the court remanded the case. On remand, the chief special master again found that "respondent proved by a preponderance of the evidence that the genetic mutation was the sole cause, principally [responsible] for Rachel's [Dravet syndrome]." No. 07-170V, 2011 WL 1135878, at *10 (Fed. Cl. Spec. Mstr. Mar. 4, 2011). As in Stone, a second motion for review was denied. 98 Fed. Cl. 719 (2011).

3. Federal Circuit Opinion in Stone/Hammitt

The foregoing decisions and opinions were the basis of the Federal Circuit's opinion in the consolidated appeals brought by Mr. and Ms. Stone as well as Mr. Hammitt. The Federal Circuit summarized the events in Amelia's medical history and Rachel's medical history as set forth above. Stone v. Sec'y Health & Hum. &

Servs., 676 F.3d 1373,1375-76 (Fed. Cir. 2012). The Federal Circuit explained that the special master had found that Amelia's and Rachel's seizure disorders were "triggered by the SCN1A gene mutation alone, and the initial febrile seizures did not result in any brain injury that caused, triggered, or rendered either child more susceptible to developing [Dravet syndrome]." Id. at 1382.

The Federal Circuit determined that a special master could consider evidence of a potentially causative factor other than the vaccination in determining whether petitioners had met their burden to present a prima facie case. In the words of the Federal Circuit, "in some cases a sensible assessment of causation cannot be made while ignoring the elephant in the room—the presence of compelling evidence of a different cause for the injury in question." Id. at 1380. In these cases, the "special master concluded that the DTaP vaccine played no role whatsoever in either child's [Dravet syndrome]." Id. at 1381.

The Federal Circuit also rejected the appellants' challenge to this factual finding due to the deferential standard of review. The Federal Circuit stated the special master could reject Dr. Kinsbourne's opinion because of his lack of recent experience in the fields of pediatric neurology and genetics. Id. at 1382. The Federal Circuit stated that the evidence supported a finding that Dr. Raymond is an expert in neurology and genetics, who was "extremely well qualified" to testify about Amelia's unusual SCN1A mutation. Id. In stating that the special master could accept Dr. Raymond's reasoning, the Federal Circuit pointed to the seven factors that Dr. Raymond considered. Id. at 1383. The Federal Circuit rejected the appellants' argument that the special master should have found that "a child's clinical condition cannot be predicted based on the [child's] SCN1A gene mutation." Id.

Separately, the Federal Circuit also addressed the special master's finding that the children did not suffer brain damage from their initial seizures. The Federal Circuit stated that the special master "merely sought evidence of the existence of brain damage—a key component of Dr. Kinsbourne's theory—and Dr. Kinsbourne was unable to provide any." Id. at 1385. This was because, in part, the clinical records showed no brain damage. Therefore, the Federal Circuit affirmed the judgments that denied compensation. Id. at 1386.

The petitioners-appellants sought a rehearing *en banc*. However, the full court denied this petition with one judge dissenting.

B. Deribeaux

Gus Deribeaux and Kimberly Burshiem alleged that a DTaP vaccine caused their daughter, Madison, to suffer a seizure disorder. Deribeaux v. Sec'y of Health & Hum. Servs., No. 05-306V, 2011 WL 6935504, at *1 (Fed. Cl. Spec. Mstr. Dec. 9, 2011). Initially, a special master found that they were entitled to compensation. Id. (citing Deribeaux v. Sec'y of Health & Hum. Servs., No. 05-306V, 2007 WL 4623461 (Fed. Cl. Spec. Mstr. Dec. 17, 2007). However, during the process for determining the amount of compensation, medical records were produced that showed Madison suffered from a genetic mutation "known to cause" Dravet's syndrome. Id. Thus, the parties developed evidence as to whether "the Secretary had rebutted Petitioners' *prima facie* case by showing that Madison's disorder was caused by an unrelated factor." Id. at *3.

Madison received the DTaP vaccine when she was seven months old in 2002. Id. The next day, she suffered a seizure and was taken to the emergency room. Id. The parties' experts agreed that this seizure was in the context of a fever. Id. at *3 n.9. While in the hospital a few days later, an EEG and MRI were normal. Id. at *3.

Madison continued to have seizures periodically and by the age of one year, her development stopped. Id. at *6. When Madison was four years old at the end of 2005, a genetic test showed that she had a mutation in her SCN1A gene. Id. at *7. This mutation arose de novo. According to the company performing the test, Athena Diagnostics, "approximately 90% of amino acid variants associated with the more severe phenotypes of SMEI or SMEB arise *de novo*, while the inherited variations are associated with milder disorders." Id. Madison's specific mutation had not previously been reported. Thus, Athena Diagnostics report stated: "it is not possible to conclude with any reasonable degree of clinical certainty at this time whether or not this variant is associated with the phenotype in question.'" Id. (citing Pet'r's Exhibit 15 at 9).

In the proceedings before the special master to determine whether the Secretary had met his burden of establishing that the genetic mutation caused Madison's Dravet syndrome, the Secretary relied primarily upon Dr. Raymond. 2011 WL 6935504 at *23. The Secretary "conceded that vaccination likely triggered Madison's first, prolonged seizure." Id. at *1. "The Secretary's theory was that Madison experienced a fever following vaccination and that the fever caused her initial, prolonged seizure. The Secretary maintained that the course of Madison's disorder was not altered or aggravated by her initial seizure, however, and that the disabilities caused by her genetic mutation would have been the same

with or without the vaccine-induced seizure." Id.; accord id. at *23-26 (summarizing Dr. Raymond's testimony).

In contrast, Mr. Deribeaux and Ms. Burshiem relied upon an opinion from a neurologist, Carlo Tornatore. Dr. Tornatore was not board-certified in genetics or pediatrics. Id. at *9. Their theory was the "vaccination not only caused Madison's initial seizure but also triggered an immune deficiency that led to . . . further neurological damage. Petitioners propounded several related theories of vaccine causation and/or aggravation, including that vaccination could precipitate a first seizure at a time when the victim was particularly vulnerable to neurological injury." Id. at *1; accord id. at *27-30 (summarizing Dr. Tornatore's testimony).

The special master denied entitlement in a decision exceeding forty pages. The thrust of the reason for the denial was set forth in the decision's introduction:

> [P]reponderant evidence demonstrated that Madison's genetic abnormality caused both her susceptibility to a post-vaccine seizure and, more importantly, her numerous subsequent seizures and other neurological problems. There is an association between Madison's initial febrile seizure and her vaccination, to be sure—the Secretary did not deny it—but no causative relationship was established between vaccination and the neurological problems that are known to occur in individuals with [Dravet syndrome].

Id. at *2.

As part of its background, the decision described Dravet syndrome. 2011 WL 6935504, at *8-9. The decision also summarized an extensive amount of literature. Id. at *12-22.

The finding that the genetic mutation was the cause of Madison's Dravet syndrome was organization around the three factors used to evaluate whether a vaccine is the cause-in-fact of a condition. Id. at *33-44. Under this test's first prong, the special master found that mutations in an SCN1A gene can cause Dravet syndrome. The special master explained:

> As evidenced by the extensive literature summarized above, both the fact of the causal association between *de novo* SCN1A mutation and [Dravet syndrome], as well as the underlying biological basis for this

> association, have been studied extensively. The medical research is well documented in the record and establishes that mutation of the SCN1A gene, without any other factor, genetic or environmental, can cause the symptoms characterized as [Dravet syndrome].

Id. at *34.

For the second prong, the special master found that the evidence showed a logical sequence of cause and effect that the mutation caused Madison's Dravet syndrome. The special master emphasized that the mutation arose de novo, credited Dr. Raymond's testimony that the mutation would impair the structure / function of the resulting protein and noted Madison's treating doctors attributed Madison's neurological problems to the genetic mutation. Id. at *35-36.

In this context, the special master extensively discussed and rejected challenges to this finding. For example, the special master found that the initial seizure did not damage Madison's brain. In making this finding, the special master credited Dr. Raymond's opinion over Dr. Tornatore's opinion because, in part, Dr. Raymond is a pediatric neurologist. Id. at *36-39. The special master also declined to credit an assertion that Madison had a "lower seizure threshold" that allowed the vaccine to trigger a seizure that would not have happened. Id. at *39-40. The special master elaborated on the structural deformity due to the gene:

> Petitioners in vaccine cases often advance the theory that individuals with unspecified genetic characteristics have a lower seizure threshold and that vaccination pushes them over the edge, resulting in a first seizure followed by further, ultimately devastating convulsions. Such an allegation might constitute a viable theory of causation if all one knew about such cases was that a child had a seizure following vaccination. But much more has been revealed by medical science in cases like Madison's. Individuals with [Dravet syndrome] have serious channelopathies that interfere with normal neuronal activity. Susceptibility to febrile seizures is only one aspect of their disorder. An initial febrile seizure is followed by more seizures of all types, with and without fever. Ataxia and developmental delay occur because of pervasive brain dysfunction. This is a known syndrome, not an isolated case of a vaccination followed by

> seizures. In light of what is known, one cannot say that Madison's neurological condition was caused by vaccination, even if her initial seizure was triggered by the vaccination. It is not Madison's seizure that caused her condition, but her condition that caused the seizure. [Dravet syndrome] would have taken its tragic toll on Madison's health whether or not she was vaccinated on March 28, 2002.

2011 WL 6935504, at *40. As part of this finding, the special master relied upon Dr. Raymond's testimony that "vital structures in Madison's brain cells were not 'built' properly because one of the building blocks (an amino acid) was effectively missing, due to the missense mutation. . . . As a result, the structure of Madison's brain cells was permanently flawed." Id. at *41.

On the third and final prong of the causation-in-fact test, the special master found that "Madison's initial seizure occurred at the time of life when such an event typically would occur in a child with [Dravet syndrome]." Id. at *43. Thus, the special master concluded: "Respondent submitted more than preponderant evidence that an alternative factor, Madison's genetic mutation, was the sole substantial cause of her neurological condition." Id. at *44. While the special master in Deribeaux denied compensation, the special master commented upon how genetics might (and might not) play a role in future cases:

> [This case's finding that a mutation caused Madison's Dravet syndrome] is not to say that medical science has all the answers to questions about [Dravet syndrome], vaccinations, and/or genetics. Genetic causation does not necessarily exclude the possibility that environmental factors may play a role in the way genes are expressed, even changing the outcome for an individual. Much more research will be needed to explore these possible interactions . . . . The possibilities for variation in individuals with [Dravet syndrome], and their cause, are complex and have yet to be explored. . . . But "definitive" proof, to borrow Dr. Tornatore's term, is not required to prove that genetic causation is more likely than not. Proof of an unrelated factor does not, under the Vaccine Act, require absolute certainty.

Id. at *32 (internal citations omitted). In a different part of the decision, the special master stated:

> There was no medical evidence that would support the contention that the mutation must be identical to one previously identified in order to produce the characteristics known to result from the type of mutation in question. Nor is it logical to require proof of an identical mutation in order to establish a chain of cause and effect between the mutation and the disorder.

Id. at *42.

Mr. Deribeaux and Ms. Burshiem challenged this decision by filing a motion for review. Preliminarily, the Court of Federal Claims rejected their argument that the special master should have elevated the Secretary's burden of proof. Deribeaux v. Sec'y of Health & Hum. Servs., 105 Fed. Cl. 583, 588-91 (2012).

As to the special master's finding of facts, the Court ruled the special master was not arbitrary in crediting Dr. Raymond's testimony over Dr. Tornatore's testimony. Id. at 591-94. The Court ruled that the special master was not arbitrary in finding that "Madison's genetic mutation was a sole substantial cause of her condition despite the fact that the vaccine triggered her initial seizure." Id. at 594. The Court also rejected petitioners' argument that "they should prevail because it cannot be said with absolute certainty that Madison, by reason of her genetic mutation, would have experienced the same symptoms even if she had not been vaccinated," because the special master "was not required to find that a conclusive one-to-one relationship existed between Madison's illness and her genetic mutation." Id. at 596. Accordingly, the Court entered judgment against petitioners.

The petitioners appealed to the Federal Circuit. In its opinion, the Federal Circuit set forth Madison's basic medical history and the case's procedural history. Deribeaux v. Sec'y of Health & Hum. Servs., 717 F.3d 1363, 1364-66 (Fed. Cir. 2013). The Federal Circuit disagreed with the appellants' contention that the special master evaluated the Secretary's claim under a standard that was too low: "The special master correctly identified that the Secretary's burden was to show a sequence of cause and effect that is logical and legally probable, although causation by the unrelated factor need not be established to a medical or scientific certainty." Id. at 1368.

As to the evidence on which the special master relied to credit the Secretary's argument that the SCN1A mutation caused Madison's Dravet syndrome, the Federal Circuit found "no basis to disturb her factual findings as arbitrary or capricious in view of both the record before us and the highly deferential standard of review under which we must conduct such an evaluation." Id. at 1369. Thus, the Federal Circuit affirmed the judgment. Id.

C. Snyder / Harris

While the Snyder and Harris cases were consolidated at the Federal Circuit, they were treated together while in the Court of Federal Claims, including the Office of Special Masters. Because the analysis was the same in both cases, only one case (Snyder) is summarized.

Jed and Lilia Snyder alleged that a DTaP vaccine given to their son, N.S., in 2005 caused him to suffer a worse form of Dravets syndrome. Snyder v. Sec'y of Health & Hum. Servs., No. 07-59V, 2011 WL 3022544, at *1 (Fed. Cl. Spec. Mstr. May 27, 2011). He received a dose of the DTaP vaccine when he was four months and experienced a seizure in the morning of the next day. Id. at *2. After a second seizure, which occurred about one month later, an EEG was normal. Id. About one year later, genetic tests showed that N.S. had a mutation in his SCN1A gene "that is diagnostic for [Dravet] syndrome." Id. at *3.

In Snyder, the (undersigned) special master set forth some basic information about how genes encode proteins and how mutations in genes may (or may not) affect the functioning of the anticipated protein. Id., at *4, 13. For the sodium channel, a proper flowing of sodium ions allows neurons to fire properly but defects in the sodium channel impair the flow of electrical impulses, causing a seizure. Id.

Mr. and Ms. Snyder presented the opinion of Dr. Kinsbourne. He opined that an "SCN1A mutation is 'not a sufficient cause in itself.'" 2011 WL 3022544, at *6 (quoting Dr. Kinsbourne's report). He also maintained that the DTaP vaccine can harm neurological development. Id.

The Secretary relied upon opinions from Dr. Raymond and a pediatric neurologist, Max Wiznitzer. While Dr. Wiznitzer generally supported Dr. Raymond's opinion that the DTaP vaccine did not harm N.S., Dr. Raymond discussed the genetic aspects more extensively. Dr. Raymond stated that the mutation in N.S.'s "SCN1A gene . . . 'is the sole cause of his epilepsy condition.'" Id. at *7 (quoting Dr. Raymond's report).

The special master's decision contained two sections of analysis (sections IV and V). In section IV, the special master found that the evidence showing the SCN1A gene was the sole cause of N.S.'s Dravet syndrome. The special master credited the opinion of Dr. Raymond in part because Dr. Raymond "is the most qualified expert to express an opinion. Dr. Raymond treats patients with genetic-based neurological disorders as part of his professional practice of medicine." Id. at *14. In reaching his conclusion that the SCN1A mutation was the sole cause of N.S.'s Dravet syndrome, Dr. Raymond reviewed four factors: "(a) the type of mutation, (b) the location of the mutation, (c) what the mutation did, that is, what amino acids were substituted, and (d) the existence of precedent cases reported in the literature." Id. (internal citations omitted). The special master found these factors supported Dr. Raymond's opinion. Id. at *15-16.

The special master also considered, but found unpersuasive, challenges to Dr. Raymond's opinion. The special master summarized literature that Mr. and Ms. Snyder had submitted but found that the literature did not persuasively support their position. Id. at *17-21. The special master rejected the opinion from Dr. Kinsbourne because he "essentially stopped practicing pediatric neurology in 1981." Id. at *21. In this context, the special master cited another special master's decision from 2000 in which that special master stated that she "really cannot rely on Dr. Kinsbourne who has had no clinical experience in ten years and does not treat [tuberous sclerosis] or any patients." Id. (citing Flanagan v. Sec'y of Health & Hum. Servs., No. 90-1126V, 2000 WL 1207256, at *13 (Fed. Cl. Spec. Mstr. Aug. 4, 2000), mot. for rev. denied, 48 Fed. Cl. 169, 173-74 (2000), aff'd sub nom., Turner v. Sec'y of Health & Hum. Servs., 268 F.3d 1334, 1338-39 (Fed. Cir. 2001)).

In summary, the special master found "N.S.'s mutation arose de novo and occurred in a conserved region of the gene, specifically a portion that codes for the pore of the sodium channel. These undisputed characteristics about N.S.'s gene meant, according to Dr. Raymond, that '[t]he alteration in his gene is the cause of his SMEI.'" 2011 WL 3022544, at *25 (citation omitted).

Section IV of the decision also discussed whether DTaP can cause a seizure disorder via two mechanisms. Id. at *25-34. One mechanism was that the acellular pertussis vaccine affects the central nervous system because, in theory, a residual portion of the pertussis vaccine is not toxoided, crosses the blood-brain barrier, and injures neurons. Id. at *27. The special master declined to evaluate this evidence because of "shortcomings in the parties' presentation." Id. at *30. A second mechanism was that the DTaP vaccine caused a fever, and a fever caused the seizure. Id. The special master rejected this mechanism because mice models

for Dravet syndrome indicated that genetically defective mice experienced seizures regardless of whether they were heated. Id. at *31-33 (citing John C. Oakley et al., Temperature-and Age-Dependent Seizures in a Mouse Model of Severe Myoclonic Epilepsy in Infancy; Frank W. Yu et al., Reduced Sodium Current in GAGAergic Interneurons in a Mouse Model of Severe Myoclonic Epilepsy in Infancy).[4] Further, Dr. Kinsbourne did not show that the initial seizure harmed N.S. Id. at *34.

The lack of damage from N.S.'s first seizure was the foundation for the finding in section V that Mr. and Ms. Snyder failed to establish that any injury lasted more than six months. Id. at *34-36. In this context, Dr. Kinsbourne was unable to say how N.S. would have been but for the vaccine. In contrast, Dr. Raymond was persuasive in explaining the vaccine did not affect his development. Consequently, the special master denied entitlement.

Mr. and Ms. Snyder sought review of the special master's decision denying them compensation. A judge from the Court of Federal Claims ruled that Mr. and Ms. Snyder had established that N.S.'s "[s]yndrome was Caused-In-Fact by the DTaP Vaccine." Snyder v. Sec'y of Health & Hum. Servs., 102 Fed. Cl. 305, 321 (2011). The Court indicated that the special master erroneously required Mr. and Ms. Snyder to present "scientific certainty," rather than "simple preponderance of evidence." Id. at 322. As support for the proposition that a DTaP vaccine can cause seizures, the Court cited the warning label for the DTaP vaccine that advises "despite detoxification, sufficient pertussis toxin may be present to trigger fever and seizures." Id.

The Court also ruled that the "Special Master Erred in Finding That The Government Demonstrated Alternative Causation." Id. at 323. The Court stated: "There is no evidence in this record, scientific or otherwise, that establishes that a child with a SCN1A mutation, *necessarily* will develop SMEI [severe myoclonic epilepsy of infancy] or another seizure disorder." Id. Later, the Court explained: "although there is a relationship between SCN1A gene mutations and SMEI, a one-to-one relationship has not been established, nor has it been determined that exposing a patient with a SCN1A mutation to acellular pertussis will have no adverse consequences." Id. at 324. The Court also viewed the value of Dr. Kinsbourne's opinion as in equipoise with the value of the opinions from Dr. Raymond and Dr. Wiznitzer. Thus, the government failed to meet its burden of proof. Id. at 325 (citing Knudsen v. Sec'y of Health & Hum. Servs., 35 F.3d 543,

[4] Complete bibliographic information for the medical articles is found in the appendix.

550-51 (Fed. Cir. 1994). The Court, accordingly, reversed the decision of the special master, found that Mr. and Ms. Snyder were entitled to compensation, and remanded the case to determine compensation. Id. at 326.

After the (undersigned) special master determined the compensation to which Mr. and Ms. Snyder were entitled and a judgment was issued, the Secretary appealed the judgment to the Federal Circuit. The Federal Circuit reversed the judgment awarding compensation and reinstated the special master's decision. Snyder v. Sec'y of Health & Hum. Servs., 553 Fed. App'x 994 (Fed. Cir. 2014) (citing Stone v. Sec'y of Health & Hum. Servs., 676 F.3d 1373, 1379 (Fed. Cir. 2012)). The Federal Circuit determined that the special master did not err in considering the record as a whole and finding that the Secretary met his burden to establish "the gene mutations were the sole cause of the seizure disorders." Id. at 1000.

With respect to the special master's factual findings, the Federal Circuit noted that Dr. Raymond and Dr. Wiznitzer were more qualified than Dr. Kinsbourne due to their differences in experience. The Federal Circuit did "not discern error in this conclusion." Id. at 1002. The Federal Circuit disagreed with the view of the Court of Federal Claims that the evidentiary value of the opinions from the experts was in equipoise. Instead, according to the Federal Circuit, the special master "made particular findings, supported by the record, in favor of the Secretary." Id. at 1003. Thus, the Federal Circuit reversed the determination of the Court of Federal Claims and reinstated the decision finding "the SCN1A gene mutation was, more likely than not, the sole cause of Petitioners' seizure disorders." Id. at 1004.

D. Other SCN1A Cases

As collected in Oliver v. Sec'y of Health & Hum. Servs., No. 10-394V, 2017 WL 747846, at *1 n.3, in numerous cases, special masters have not credited the claim that a childhood vaccination caused a seizure disorder when the child had a mutation in the SCN1A gene.[5] As indicated in the parentheticals, in some cases petitioners voluntarily dismissed their petitions and the decisions in those cases are

[5] Oliver lists Sucher v. Sec'y of Health & Hum. Servs., 07–58V, 2010 WL 1370627 (Fed. Cl. Spec. Mstr. Mar. 15, 2010), as among the cases in which special masters did not award compensation. However, Oliver's cite to Sucher is mistaken because the special master found that the petitioners were awarded compensation. 2010 WL 1370627, at *45. Sucher's value is nevertheless limited because the child in Sucher was not found to have a genetic mutation, although Dr. Kinsbourne assumed she had one.

relatively short (two or three pages). In other cases, the parties fully litigated the case, leading to much longer decisions by special masters. Some, but not all, of those determinations were the subject of a motion for review. When a motion for review was filed, the decision denying compensation was found not arbitrary.

A list of those cases, presented in chronological order starting with the earliest, includes:

No.[6]	Name and Citation	Appellate Review
4	Craner v. Sec'y of Health & Hum. Servs., 10–475V, 2011 WL 6401290 (Fed. Cl. Spec. Mstr. Oct. 27, 2011) (decision granting petitioners' motion to dismiss their petition after the SCN1A mutation was discovered)	
5	Barnette v. Sec'y of Health & Hum. Servs., 06–868V, 2012 WL 5285414 (Fed. Cl. Spec. Mstr. Sept. 26, 2012)	mot. for rev. den'd, 110 Fed. Cl. 34 (2013)
6	Schniegenberg v. Sec'y of Health & Hum. Servs., 13–347V, 2014 WL 4674382 (Fed. Cl. Spec. Mstr. Apr. 29, 2014) (decision dismissing case after petitioners failed to present any evidence after the SCN1A mutation was brought forward in litigation)	
7	McHerron v. Sec'y of Health & Hum. Servs., 07-753V, 2014 WL 3360324 (Fed. Cl. Spec. Mstr. June 18, 2014) (decision granting petitioners' motion to dismiss their petition after testing revealed their child had an SCN1A mutation)	
8	Mathis v. Sec'y of Health & Hum. Servs., 09-467V, 2014 WL 3955650 (Fed. Cl. Spec. Mstr. July 24, 2014) (decision granting petitioner's motion to dismiss her petition after testing revealed her child had an SCN1A mutation)	

[6] The numbering begins with "four" to account for the three cases (Stone, Deribeaux, and Snyder) that were already discussed. Because Stone was consolidated with Hammitt and because Snyder was consolidated with Harris, the list could have started with "six."

9	Waters v. Sec'y of Health & Hum. Servs., 15–320V, 2015 WL 3898079 (Fed. Cl. Spec. Mstr. June 4, 2015)	
10	Santini et al. v. Sec'y of Health & Hum. Servs., 06–725V, 2014 WL 7891507 (Fed. Cl. Spec. Mstr. Dec. 15, 2014)	mot. for rev. den'd, 122 Fed. Cl. 102 (2015)
11	Barclay ex rel. Ramirez v. Sec'y of Health & Hum. Servs., 07–605V, 2014 WL 7891493 (Fed. Cl. Spec. Mstr. Dec. 15, 2014)	mot. for rev. den'd, 122 Fed. Cl. 189 (2015)
12	Faoro v. Sec'y of Health & Hum. Servs., 10–704V, 2016 WL 675491 (Fed. Cl. Spec. Mstr. Jan. 29, 2016)	mot. for rev. den'd, 128 Fed. Cl. 61 (2016)

Other than their consistency in outcome, these cases carry less precedential weight. None of them reached the Federal Circuit.

E. Oliver

The fourth SCN1A case to reach the Federal Circuit was initiated by Laura and Eddie Oliver on behalf of their son, E.O. They alleged that various vaccines, including the DTaP vaccine given to E.O. in 2009, caused him to develop a fever and febrile seizures. Oliver v. Sec'y of Health & Hum. Servs., No. 10-394V, 2017 WL 747846, at *1 (Fed. Cl. Spec. Mstr. Feb. 1, 2017).

E.O. had a mutation in his SCN1A gene. Id. at *1, *6. E.O. received his vaccinations as part of a six-month well-child exam. Id. at *4. He experienced his first seizure, which was febrile, the same day. Id. at *4, *17 n.47. After about one year in which his seizures increased in frequency, a genetic test showed that he had a mutation in his SCN1A gene that neither parent carried. Id. at *6. The report from Athena Diagnostics, Inc. characterized the mutation as of "unknown significance." Id. at *7 n.10. However, a database from China reported a child with an identical mutation who also had Dravet syndrome. Id. at *7, *18.

Mr. and Ms. Oliver advanced their claim by retaining a pediatric neurologist, Yuval Shafrir. Id. at *10. His theory, in essence, was "the SCN1A mutation made E.O. susceptible to developing Dravet syndrome, that a gene-environmental interaction is at play, and that the vaccinations trigger that interaction." Id. at *1.

The Secretary responded with reports from Dr. Raymond, as well as one report from a neurologist specializing in pediatric epilepsy, Rajesh Sachdeo. Id. at

*11. Their view was that "E.O.'s mutation is the sole cause of his Dravet syndrome and his resulting neurological condition." Id. at *1.

In discussing how a DTaP vaccine can cause Dravet syndrome, Dr. Shafrir acknowledged that "the SCN1A mutation is a necessary cause of Dravet syndrome, but he opine[d] that the mutation alone is not sufficient to cause the disease." Id. at *12. Dr. Shafrir proposed two mechanisms to bring forth Dravet syndrome in a vulnerable person: either "second hit" or an immune-mediated reaction (molecular mimicry). Id. at *12-13.

However, Dr. Raymond disagreed and offered a threefold response:

> First, the existing medical studies and literature have established that a significant alteration in the SCN1A gene alone is sufficient to cause Dravet syndrome . . . . Second, animal models have demonstrated significant abnormalities of SCN1A mutation that "mirror the human condition," and in these studies the animals spontaneously developed seizures without any triggers . . . . Third, the McIntosh et al. and Berkovic et al. studies show that the occurrence of febrile seizures following vaccinations does not change the clinical course or outcome of Dravet syndrome.

Id. at *15 (internal citations omitted).

The special master found that Mr. and Ms. Oliver had failed to meet their burden of proof. The special master explained:

> [T]he existing medical literature has established that vaccination does not affect the clinical course or prognosis of Dravet syndrome. The animal models, as presented by Dr. Raymond, provide strong evidence that Dravet syndrome will develop in children with the SCNIA mutation, whether or not they receive vaccinations.

2017 WL 747846, at *16.

In addition to finding Mr. and Ms. Oliver's proof lacking for Althen prong one, the special master determined that they had not established Althen prong two. Id. at *16-21. For Althen prong three, the special master found that the onset of

seizures within twenty-four hours of vaccination was not sufficient for finding that the vaccination caused the Dravet syndrome that was diagnosed twenty-one months later. Id. at *20-21.

Besides finding that Mr. and Ms. Oliver did not meet their burden to show causation-in-fact, the special master found that they failed to establish a vaccine significantly aggravated E.O.'s epilepsy. Id. at *22-24; id. at 24 (noting that "the vaccinations did not change his clinical course and thus did not significantly aggravate his preexisting condition"). The special master reached this outcome because of the overlap in the elements under both causes of action.

Likewise, the special master found that the Secretary "has put forth preponderant evidence establishing that E.O.'s SCN1A mutation, a factor unrelated to the administration of the vaccines, is the agent solely responsible causing his Dravet syndrome." Id. at *26. The special master analyzed that issue by looking at the elements from Althen's causation-in-fact test. For the first prong, the special master stated: "The medical articles and studies filed in this case establish that the international medical community generally agrees that vaccinations are not the cause of Dravet syndrome and that the SCN1A mutation is responsible for causing the disease." Id. The special master credited Dr. Raymond's testimony that the type of mutation present in E.O., a splice-site mutation, causes "no protein production and thus causes disease." Id. at *27.

For the second prong, the special master recounted the testimony of Dr. Raymond and Dr. Sachdeo that even if E.O.'s seizures started earlier because of the vaccine, an earlier onset of E.O.'s seizure disorder would not have changed his outcome. 2017 WL 747846, at *27. The special master accepted these opinions as consistent with the McIntosh and Brunklaus articles.

Finally, with respect to timing, the special master noted that:

> E.O. had no encephalopathy after the vaccinations at issue. Therefore, E.O. did not have an injury that was temporally associated with the vaccines on April 9, 2009. His initial seizure was, in hindsight, a suspicious sign that he might develop Dravet syndrome, or the initial manifestation of his genetic mutation. That fact alone does not establish a vaccine-related injury.

Id. at *27. Therefore, based upon these findings, the special master found that the Secretary met his burden to show that the mutation, not the vaccination, was the sole cause of E.O.'s Dravet syndrome. Id.

Mr. and Ms. Oliver filed a motion for review. A judge from the Court of Federal Claims denied the motion, essentially because the factual findings were not arbitrary. Oliver v. Sec'y of Health & Hum. Servs., 133 Fed. Cl. 341 (2017). The judge stated:

> The Chief Special Master carefully considered the entire record, including the opinions of the experts and the medical literature. She explained her reasoning in detail. Under the well-established principles set forth above, this Court defers to the Chief Special Master's ultimate conclusion that the opinions of the government's experts were more persuasive than those of Dr. Shafrir, and that E.O.'s SCN1A gene mutation and not a vaccine was the cause of E.O.'s Dravet syndrome.

Id. at 354. Thus, judgment was entered against Mr. and Ms. Oliver.

Mr. and Ms. Oliver continued the litigation by appealing to the Federal Circuit. The panel of Federal Circuit judges split with a majority affirming the judgment to deny compensation. Oliver v. Sec'y of Health & Hum. Servs., 900 F.3d 1357 (Fed. Cir. 2018). The majority characterized the appellants' argument as "no more than a challenge to the weight afforded to their expert's testimony and supporting evidence." Id. at 1361. The Federal Circuit determined that the "factual findings were neither arbitrary nor capricious," and under the standard of review, the Federal Circuit "cannot review such challenges." Id. at 1362. Thus, the judgment was affirmed.

However, one judge from the Federal Circuit dissented. In this judge's view, the medical studies "show that both vaccination and the mutation have a role in Dravet syndrome." Id. at 1365 (Newman, J., dissenting). The dissenting judge stated:

> Science is at last providing answers to why some infants manifest a severe reaction to vaccination. However, these are the infants for whom the Vaccine Act was enacted. Instead, HHS and the courts now exclude these

> infants from the Vaccine Act—in contravention of the statute and the legislative purpose.

Id. at 1365.

The dissenting judge summarized eight articles, including the McIntosh and Berkovic articles. According to this jurist, these articles showed "continuing uncertainties" about "the role of vaccination when the SCN1A mutation is present." Id.

With respect to the facts for E.O., the dissent stated that: "It is not known whether E.O. would have manifested Dravet syndrome without the vaccination. The only certainty is that E.O. experienced a dramatic reaction within a few hours of DTaP vaccination, that the seizures continued, and that there were developmental consequences." Id. at 1369. In the dissent's view, the special master erred in finding that "neither that initial seizure nor his vaccinations caused his Dravet syndrome or neurological complications." Id. (citation omitted).

After the panel from the Federal Circuit ruled against Mr. and Ms. Oliver, they sought rehearing from the panel and a rehearing *en banc*. The Federal Circuit denied this petition. Oliver v. Sec'y of Health & Hum. Servs., 911 F.3d 1381 (Fed. Cir. 2019).

But, two judges from the Federal Circuit dissented from the rehearing *en banc*. The dissent began with a statement from the legislative history of the Vaccine Act that indicates a small number of children will be injured by a vaccine but predicting who will be injured "is not always possible." Id. at 1382 (Newman, J., dissenting) (citing H.R. Rep. No. 99-908, at 4-6 (1986), *as reprinted in* 1986 U.S.C.C.A.N. 6344, 6345-46)). The dissent objected to the conclusion that "E.O. would have been gravely injured due to his SNC1A mutation—that it is his 'destiny'—and that it is irrelevant that the DTaP vaccinations initiated the seizures and their consequences." Id. at 1383.

In the dissent's view, advances in genetics, "'vaccinomics' and 'adversomics'" will, in the future, help doctors predict which children might be harmed by a vaccination. Id. at 1384. But, until doctors test children's genetic mutations before the vaccination, a genetic test should not be the basis for an award of compensation. Finally, the dissent called upon an *en banc* review to correct the flawed outcomes in Snyder, Deribeaux, and Stone. Id. at 1385-86.

F. Sharpe

Although not an SCN1A case, the next precedent from the Federal Circuit involving a genetic mutation in a vaccinated child is Sharpe. Sharpe is the case on which Mr. and Ms. Vinesar rely most heavily.

Sharpe began when Heidi Sharpe alleged that a vaccination with DTaP and other vaccines on February 10, 2011 significantly aggravated a central nervous system disorder affecting her child, L.M. Sharpe v. Sec'y of Health & Hum. Servs., No. 14-65V, 2018 WL 7625360, at *1 (Fed. Cl. Spec. Mstr. Nov. 5, 2018).[7] In 2016, Ambry Genetics determined that L.M. possessed a mutation in the DYNC1H1 ("DYNC") gene. Id. at *5. According to Ambry Genetics, the mutation "is the cause of [L.M.'s] clinical symptoms." Id. One reason for this finding is that another female patient with the "same mutation . . . experienced a phenotypic outcome very similar to L.M's course." Id. However, Ambry Genetics also stated that "'[n]o clear genotype-phenotype correlations have emerged, although alterations associated with malformations of cortical development tend to cluster in the motor domain, whereas alterations associated with SMA-LED [spinal muscular atrophy with lower extremity predominance] tend to cluster in the stem domain.'" Id. (quoting Ambry Genetics Rep., at 40).

The symptoms to which the Ambry Genetics report referenced started no later than four days after the vaccination when L.M. had a seizure without a fever. Id. at *2. An EEG showed that L.M. had hypsarrhythmia, which is characteristic for a condition known as infantile spasms. Id. at *3. L.M. experienced significant delays in her development, delays that are common in infantile spasms. Id.

To connect L.M.'s disorder to the vaccines she received, Ms. Sharpe retained two experts. The first was Robert Shuman, a pediatric neuropathologist. Id. at *7-12. Because Dr. Shuman formed his opinions before L.M.'s genetic mutation was detected, he largely did not discuss that topic. Id. at *12; see also id. at *8 (noting that "[t]he core of Dr. Shuman's testimony and opinion was his interpretation of L.M.'s various MRI's"). The genetic issues were mostly left for Ms. Sharpe's second expert, Dr. Boles. Id. at *12-15. The main thrust of Dr. Boles's opinion was differentiating mutations in the stem (or tail) part of the gene from mutations in other parts of the gene responsible for motor function. In Dr. Boles's opinion, a mutation in the tail was "far more likely to experience a severe

[7] Ms. Sharpe also alleged that L.M. suffered an injury appearing on the Vaccine Table, encephalitis. However, this allegation is not further discussed in the present decision because Mr. and Ms. Vinesar have not claimed an on-Table injury.

outcome than one with a mutation in the stem." Id. at *13. Because L.M.'s mutation was in the stem and because she had a severe outcome, something else (a vaccine) made L.M.'s condition worse.

The Secretary also retained two experts. One was a pediatric neurologist with extensive experience treating infantile spasms, John Zempel. 2018 WL 7625360 at *19, *22 n.36. Dr. Zempel opined "L.M.'s history to constitute a 'classic presentation' of an infantile spasm disorder only temporally coinciding with the vaccines she received in February 2011." Id. at *21. He briefly added that the DYNC gene mutation was "more likely the cause of L.M.'s condition." Id. at *22.

The Secretary's other expert, Maria Descartes, focused on the genetic issues because she is board-certified in genetics and pediatrics. Id. at *16. Dr. Descartes stated that de novo mutations in conserved regions are more frequently associated with severe outcomes. Id. at *17. "However, she also acknowledged that it could not be predicted in advance with complete certainty what *any* outcomes would be for individuals bearing DYNC mutations, and that the possession of certain mutations was not necessarily determinative of outcome." Id. Dr. Descartes also responded to Dr. Boles's opinion regarding the location of the mutation by maintaining that "a range of outcomes was always possible regardless of mutation location." Id.

At the beginning of the special master's analysis of the evidence, the special master discussed the (older) whole cell version of the pertussis vaccine ("DTP") and the (current) acellular version of the pertussis vaccine ("DTaP"). Although Kottenstette v. Sec'y of Health & Hum. Servs., No. 15-1016V, 2017 WL 6601878 (Fed. Cl. Spec. Mstr. Dec. 12, 2017) "elide[d]" the differences between them, this special master stated that "there *is* a significant distinction between the DPT vaccine and the subsequent forms that use the acellular version of pertussis." Sharpe, 2018 WL 7625360, at *31. In support of this proposition, the special master cited a series of cases from special masters, starting with Grace v. Sec'y of Health & Hum. Servs., No. 04-[redacted], 2006 WL 3499511, at *9 (Fed. Cl. Spec. Mstr. Nov. 30, 2006).

When considering how the DTaP might have harmed L.M., the special master most importantly found that Ms. Sharpe "did not successfully establish that L.M.'s post-vaccination condition was sufficiently worse to constitute a 'significant aggravation' of her DYNC mutation." Id. at 36 (capitalization changed without notation). As part of the third prong of Loving, the special master held that a "claimant must demonstrate that his or her post-vaccination condition is

overall *qualitatively* worse than what would be expected given what is known about the preexisting condition (which might otherwise have deleterious effects on its own)." Id. at 36 (citing Locane v. Sec'y of Health & Hum. Servs., 685 F.3d 1375, 1381-82 (Fed. Cir. 2012)). In interpreting the law regarding significant aggravation, the special master held that he or she must evaluate "what is known about the preexisting mutation and its likely impact on an affected individual's life." Id. at *37. The special master found that "L.M.'s overall course is consistent with what is known about the effects of a DYNC mutation. The evidence therefore does not preponderate in favor of the conclusion that L.M.'s spasm disorder otherwise attributable to her DYNC mutation was worsened by vaccination." Id.

With respect to the DYNC mutation, the special master declined to credit Dr. Boles's opinion regarding the significance of location of the mutation. Although the special master found that Dr. Boles's opinion "raised interesting and valid scientific points," it was ultimately "flawed." Id. at *38. One reason for rejecting Dr. Boles's opinion was the example of another patient, noted in the Ambry Genetics report and subsequently described in an article by Helbig, with "the *precise* same amino acid alteration location as L.M., and an outcome comparable to that experienced by L.M." Id. at *39.

For Loving's fifth prong, the special master found that the vaccinations did not worsen L.M.'s seizure disorder. The special master recognized that L.M.'s infantile spasms became more obvious after the vaccination. But, this sequence did not establish that the vaccinations caused any worsening. Id. at *41 (noting that although the petitioner's experts "found particularly compelling the fact that L.M.'s West syndrome became most obvious after vaccination" it remains "axiomatic in the Vaccine Program that a mere temporal relationship between vaccination and illness does not establish causation"). Accordingly, for these reasons, the special master denied compensation. The special master also stated, in a footnote, that if Ms. Sharpe had met her burden to present a prima facie case, then the Secretary had met his burden to establish a factor unrelated to the vaccine (the genetic mutation) caused L.M.'s condition. Id. at *37 n.47. In this lengthy footnote, the special master analogized the DYNC gene to the SCN1A gene.

Ms. Sharpe filed a motion for review. Regarding her significant aggravation claim, Ms. Sharpe argued that the special master "erred because he 'unambiguously required [the petitioner] to predict [L.M.'s] current condition' had L.M. not been vaccinated." Sharpe v. Sec'y of Health & Hum. Servs., 142 Fed. Cl. 630, 645 (2019) (quoting petitioner's Motion for Review).

The judge from the Court of Federal Claims disagreed, stating that Ms. Sharpe's argument did not present "a fair reading of the decision." Id. In the judge's view:

> [T]he Special Master had to evaluate what can be attributed to her genetic mutation and what impact the mutation would have on her life without the vaccinations. Assessing an off-Table significant aggravation claim therefore necessarily involves asking whether the individual's "clinical course and outcome [would have been] any different than it would have been if [she] had not been vaccinated[.]"

Id. (quoting Oliver v. Sec'y of Health & Hum. Servs., No. 10-394V, 2017 WL 747846, at *23). In assessing this issue, the Court ruled that the special master "reasonably determined that L.M. was not guaranteed a mild outcome. Rather, her outcome, as demonstrated by the medical literature, was consistent with children who experienced infantile spams and specifically the condition of another little girl with the same genetic mutation." Id. at 645.

The Court also indicated that the special master alternatively found that the Secretary had met his burden regarding the factor unrelated. But, the Court, itself, did not review this finding because the special master's primary finding (that Ms. Sharpe had not met her burden) was based upon the "entire record" and a "rational conclusion." Id. at 646-47. Thus, the Court affirmed the judgment denying compensation.

Ms. Sharpe appealed the judgment to the Federal Circuit. With respect to the third Loving prong, which concerns comparing the vaccinee before and after the vaccination, the Federal Circuit held that the special master erred. Based upon Whitecotton v. Sec'y of Health & Hum. Servs., 81 F.3d 1099, 1105 (Fed. Cir. 1996), the Federal Circuit held that the special master made a mistake in requiring "a petitioner to demonstrate an expected outcome and that her current-post vaccination condition was worse than such expected outcome." Sharpe v. Sec'y of Health & Hum. Servs., 964 F.3d 1072, 1081 (Fed. Cir. 2020). The Federal Circuit, however, allowed that a special master "should consider all evidence in the record, including evidence of other possible sources of injury." Id. at 1082. And a special master may find that a vaccinee's "condition 'was not affected by the vaccination.'" Id. (quoting Locane, 685 F.3d at 1378).

The Federal Circuit's panel in Sharpe was concerned about requiring a petitioner to present information about an expected outcome in a gene mutation cases because, according to this panel, "a clinical outcome is nearly impossible to predict." Id. at 1082. For this proposition, the Federal Circuit quoted testimony from the Secretary's expert in genetics, Dr. Descartes. She testified:

> The dream of the geneticist is to find genotype-phenotype correlation, because when a parent comes to talk to me, the first thing they want to know, is my child going to be able to do this and that? How long my child is going to live? Do you have any answer to these questions? The mutation that you found, what do you know? And the answer, unfortunately, to all these questions that parents ask all the time is we don't know.

Id. at 1082 (internal citation omitted).

As to Loving's fourth prong, the Federal Circuit stated that the special master found that Ms. Sharpe had not met her burden of proof due to the presence of the Ambry patient. The Federal Circuit held that the special master's factual finding was "arbitrary and capricious and must be set aside." Id. at 1084.

The flaw in relying upon the Ambry / Helbig patient was:

> [n]either party established whether the Ambry patient faced any of the same environmental factors that arguably affected the outcome of L.M.'s mutation, including vaccination. If the Ambry patient was also vaccinated, then the patient's condition could also have been caused by her vaccine. Additionally, even if the Ambry patient suffered from the same condition as L.M. without vaccination, a single example cannot establish the typical progression of a disease; nor is such a singular example sufficient to disprove a medical theory that a vaccine can cause aggravation in some patients.

Id. at 1084. In this context, the Federal Circuit criticized the special master for determining that "L.M. was destined to have a severe outcome" noting that a "deterministic mindset does not belong in the Vaccine Injury Program." Id. For this proposition, the Federal Circuit cited the opinion dissenting from the denial of

rehearing *en banc* in Oliver v. Sec'y of Health & Hum. Servs., 911 F.3d 1381, 1384 (Fed. Cir. 2009). Id., n.4.

For Loving's fifth prong, the Federal Circuit again ruled that the special master erred in his analysis. (It is not readily apparent whether the special master's mistake on prong five was an error of law or an error of fact.) The Federal Circuit set aside the special master's finding without making one of its own. Id. at 1086 (noting the fact "that L.M. experienced some seizure episodes before receiving her vaccination should have no negative affect on Petitioner's case").

Finally, the Federal Circuit addressed the special master's alternative determination that the gene mutation was "the sole, substantial factor in causing L.M.'s seizure disorder." Id. The Federal Circuit found that the "record does not support this finding." Id. Here, the Federal Circuit summarized the evidence regarding a mutation in the stem region of the gene. The Federal Circuit found that the "science in the record uniformly supports . . . [a finding that] a stem mutation in the DYNC1H1 gene is generally more likely than not going to lead to a non-severe, non-cognitive disorder." Id. at 1087. Therefore, "there is no substantial evidence to support the conclusion that L.M.'s stem mutation was *more likely than not* the *sole, substantial* factor causing her severe seizure disorder." Id.

For these reasons, the Federal Circuit vacated the special master's decision regarding the off-Table claim. The Federal Circuit remanded for further proceedings. Id. However, before the mandate issued, the Secretary sought a panel rehearing or a rehearing *en banc*. A thrust of this argument was that the panel erred in relying upon Whitecotton because Whitecotton was an on-Table case and Ms. Sharpe as well as Locane are off-Table cases.[8] Resp't's-Appellee's Pet. for Rehear'g and Rehear'g *en Banc*, No. 2019-1951, at 13 (Fed. Cir. filed Sept. 8, 2020). However, after inviting and receiving a response from Ms. Sharpe, the Federal Circuit denied the petition for a rehearing *en banc*. Sharpe v. Sec'y of Health & Hum. Servs., No. 2019-1951 (Fed. Cir. 2020).

When Sharpe returned to the special master, he found that the Federal Circuit's opinion "unquestionably forecloses further consideration of Respondent's success in establishing alternative cause/factor unrelated based on the DYNC

[8] The amount of evidence in on-Table cases differs from the amount of evidence in off-Table cases. The Vaccine Act "'relaxes proof of causation for injuries satisfying the Table, . . . but does not relax proof of causation in fact for non-Table injuries.'" Boatmon v. Sec'y of Health & Hum. Servs., 941 F.3d 1351, 1359 (Fed. Cir. 2019) (ultimately quoting Grant v. Sec'y of Health & Hum. Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992)).

mutation." Sharpe v. Sec'y of Health & Hum. Servs., No. 14-65V, 2021 WL 1291720, at *6 (Fed. Cl. Spec. Mstr. Feb. 19, 2021). On the question that the Federal Circuit left open, Loving prong 5, the special master relied on L.M.'s transient reaction on the day of the vaccination and her seizure days later. Id. at *7. While characterizing this evidence as "quite thin" and "weak[]," the special master found that Ms. Sharpe met her burden. Id. at *7-8. In this context, the special master distinguished L.M.'s genetic mutation from mutations in the SCN1A gene because less is known about the DYNC mutation. Id. at *8; see also id. (noting that the "admitted little that is still known about the DYNC mutation and its possible interaction with vaccines is to no small extent another factor favoring Petitioner"). Accordingly, the special master ruled that Ms. Sharpe was entitled to compensation and ordered the parties to proceed to damages. Id. at *9.

G. Sanchez

Although not cited by the parties, the Federal Circuit's 2022 opinion in Sanchez is arguably more important than Sharpe. In a 2020 opinion in Sanchez, the Federal Circuit vacated an October 9, 2018 decision that had led, after the denial of a motion for review, to a judgment against Germain and Jennifer Sanchez. A primary reason for the Federal Circuit's vacatur was a significant discrepancy in the [undersigned] special master's finding of fact regarding the neurological health of the Sanchezes' child, Trystan, in mid-February 2009. Sanchez v. Sec'y of Health & Hum. Servs., 809 F. App'x 843, 853 (Fed. Cir. 2020). Trystan's activities in mid-February 2009 were important because Trystan received a DTaP vaccination on February 5, 2009. Id. at 845. The Sanchezes and the two experts whom they retained maintained that by mid-February 2009, Trystan was displaying unusual arm movements that (a) were brought about by the vaccination and (b) marked an early manifestation of a condition with which Trystan was eventually diagnosed, Leigh's syndrome. See, e.g., Sanchez v. Sec'y of Health & Hum. Servs., No. 11-685V, 2020 WL 5641872, at *8 (Fed. Cl. Spec. Mstr. Aug. 26, 2020).

In contrast, the Secretary and the experts whom he retained contended that Trystan did not have any unusual arm movements, or, if there were unusual arm movements, they were not associated with Leigh's syndrome. Acting through Dr. Raymond, the Secretary also argued that Trystan's Leigh's syndrome was solely caused by mutations in a gene known as the SDHA gene. Id. at *1.

After the Federal Circuit's 2020 Opinion, the special master's August 26, 2020 decision focused predominantly on evaluating whether the Sanchezes established that the DTaP vaccination caused Trystan to develop Leigh's

syndrome. Id. at *20-51. The special master found that the Sanchezes did not meet their burden of proof under Althen. One reason was that Trystan did not display symptoms of Leigh's syndrome in mid-February 2019, which was an assertion underpinning their expert's opinions. Id. at *24, *28. Another reason was that Trystan's treating doctors linked his Leigh's syndrome to the genetic mutation. Id. at *50-51 (discussing Dr. Haas and Dr. Wong, a geneticist).

Although unnecessary to the outcome, the special master also evaluated the parties' evidence regarding the role of Trystan's genetic mutations. Id. at *56-61. As part of this analysis, the special master placed the burden of proof on the Secretary to establish "'that the factor unrelated, not the vaccination, actually caused the injury alleged.'" Id. at *53 (quoting Deribeaux v. Sec'y of Health & Hum. Servs., 717 F.3d 1363, 1369 (Fed. Cir. 2013)). In this context, the special discussed Rachel Hammitt's case in which the Federal Circuit ruled that the special master was not arbitrary in crediting Dr. Raymond's opinion. Id. at *54 (citing Stone v. Sec'y of Health & Hum. Servs., 676 F.3d 1373 (Fed. Cir. 2012)). The special master also discussed L.M.'s case in which the Federal Circuit ruled that the special master's finding that "the genetic mutation was the likely sole substantial factor causing L.M.'s severe seizure disorder was not supported by substantial evidence." Id. at *55 (citing Sharpe v. Sec'y of Health & Hum. Servs., 964 F.3d 1072 (Fed. Cir. 2020) (noting the "record did not support the special master's conclusion because the specific mutation in L.M. 'generally result[s] in non-severe, noncognitive disorders.'")).

As to the significance of Trystan's two SDHA mutations, the parties' retained experts differed. Dr. Raymond's opinion was that the gene mutations entirely explained Trystan's condition and for this proposition Dr. Raymond relied primarily upon an article by Parfait. Id. at *56; see Beatrice Parfait et al., Compound Heterozygous Mutations in the Flavoprotein Gene of the Respiratory Chain Complex II in a Patient with Leigh Syndrome, 106 Human Genetics 236 (2000). The geneticist whom the Sanchezes retained, Dmitriy Niyazov, stated the "genetic mutations were not sufficient, by themselves, to cause [Trystan] to suffer Leigh's syndrome." Sanchez, 2020 WL 5641872, at *56. Instead, a second stressful event, such as a vaccination, was also needed. Id.; see also id. at *15 (describing Dr. Niyazov's qualifications). These experts extensively discussed six articles, which the special master summarized. Id. at *56-57. Based upon this evidence, the special master found that the Secretary carried his burden to present preponderant evidence. Id. at *58. In doing so, the special master recognized that Dr. Niyazov offered strong points. On the other hand, the

Secretary's burden was merely to present a persuasive case, not necessarily a clear and convincing case. Id.

A reason for crediting Dr. Raymond was that the Parfait article reported the case of a child with two genetic mutations of which one was exactly the same as Trystan's and the other was similar and the child in the Parfait article also developed Leigh's syndrome. Id. at *59. The authors of the Parfait also experimented to determine the "'deleterious effect'" of one mutation. Id. (quoting Parfait, at 241). The special master also found unpersuasive Dr. Niyazov's criticisms of the Parfait article because Dr. Niyazov appeared to be demanding scientific certainty "that exceeds the preponderance of the evidence standard." Id. A second reason for crediting Dr. Raymond's opinion was the methodology he used in analyzing Tristan's genetic mutation matched his methodology in Rachel Hammitt's case. Notably, the Federal Circuit appeared to support this methodology when determining that the special master reasonably relied upon Dr. Raymond's opinion in Stone, 676 F.3d 1373. See id. at *60. Finally, as noted above, two doctors stated that Trystan suffered from a genetic disease. Id. at *61. Accordingly, the special master found: "Trystan's compound heterozygous mutations are the sole substantial cause of his Leigh's syndrome." Id.

Mr. and Ms. Sanchez filed a motion for review. The judge found that the special master's finding about the lack of neurological symptoms in mid-February was not arbitrary. Sanchez v. Sec'y of Health & Hum. Servs., 152 Fed. Cl. 782, 807 (2021). However, the judge of the Court of Federal Claims declined to review the findings regarding genetics. Id. at 799. Thus, judgment was entered against the Sanchezes.

For a second time, the Sanchezes appealed to the Federal Circuit. The Federal Circuit's panel divided. The majority ruled in favor of Mr. and Ms. Sanchez. Sanchez v. Sec'y of Health & Hum. Servs., 34 F.4th 1350 (Fed. Cir. 2022). The majority's analysis was divided into two parts. First, the majority determined that the special master's fact finding regarding a lack of neurologic problems in mid-February 2009 was not logical. Because this was the foundation for the special master's finding that the Sanchezes did not establish their causation-in-fact case, the special master's determination was reversed. Id. at 1354-56.

Second, the majority addressed the special master's alternative finding regarding genetics. The majority stated: "There is no evidence . . . that Trystan's mutations would have resulted in the same progression and severity of his Leigh's syndrome absent the vaccine." Id. at 1356. Quoting Sharpe v. Sec'y of Health & Hum. Servs., 964 F.3d 1072, 1084 (Fed. Cir. 2020), the majority stated that "a

single example does not establish the typical progression of a disease and is not 'sufficient to disprove a medical theory that a vaccine *can* cause aggravation in *some* patients.'" Id. The majority, accordingly, found that the Sanchezes were entitled to compensation and remanded for damages.

The dissenting member's opinion disagreed with the majority's evaluation of the special master's fact-finding regarding Trystan's condition in mid-February 2009. The dissent explained:

> given the competing evidence regarding the etiology of Trystan's condition, it was not unreasonable for the special master to conclude that Trystan's Leigh's syndrome did not manifest itself until significantly later than the date of his February 2009 vaccinations, and therefore that no causal relationship was established between the vaccinations and the triggering of Trystan's Leigh's syndrome.

Id. at 1360 (Bryson, J., dissenting). Like the judge of the Court of Federal Claims, the dissent did not comment on the genetics issue.

II. Events in A.V.'s Life

A. Before Allegedly Causal Vaccination

A.V. was born on September 23, 2014. Exhibit 9 at 25. Testing at birth was normal. Id. at 25-33. However, according to a test report from approximately three years later, A.V. suffered from two mutations in a gene, known as the SCN1A gene. Exhibit 4 at 2. One of the polymorphisms was "consistent with the diagnosis of an SCN1A-related disorder." Id. Dr. Raymond opines that this genetic problem is the basis for A.V.'s seizure disorder. Exhibit A at 6 (noting that "a mutation in her SCN1A gene . . . is the sole cause of her epilepsy condition.") In contrast, Dr. Boles opines that this genetic problem made A.V. vulnerable to developing a condition. Exhibit 153 at 1.

Throughout her first six months of life, A.V. was developing normally and meeting her milestones. Exhibit 11 at 30-40.

B. Vaccination and First Seizure

As part of A.V.'s well-baby appointment for six-month-old children, A.V. received the third round of the standard set of childhood vaccines, including DTaP.

Exhibit 8 at 1 (Apr. 20, 2015). The time of vaccination was approximately 10:00 A.M. Exhibit 11 at 30. A.V. was given Tylenol prophylactically. According to Ms. Vinesar's declaration, filed on March 23, 2018, A.V. slept more than usual. Exhibit 1.

At approximately 11:30 P.M. that day, A.V. suffered a seizure and an ambulance was called. Exhibit 3-1 at 31. The emergency medical technicians recorded that A.V.'s temperature was 102 degrees Fahrenheit. Exhibit 19 at 30. Medical personnel gave A.V. a sedative, Versed 1.8 mg, to control the seizure. Exhibit 3-1 at 32.

In the emergency department of Lutheran Hospital, A.V. had another seizure. Id. Her temperature was 38.4 degrees Celsius (101.1 degrees Fahrenheit). Id. An EEG and CT scan was normal. Exhibit 3-2 at 75-76. Testing on blood cultures did not reveal any infections. Id. at 82, 85-88.

The doctors admitted A.V. to the hospital. The diagnosis was complex febrile seizures because the seizures lasted more than fifteen minutes. Exhibit 3-2 at 78. The doctors indicated that the vaccinations from earlier that morning were "the most likely source of her fever." Exhibit 3-1 at 37.

Dr. Mohammad Ikramuddin discussed A.V.'s seizures "in detail with the family, including mechanisms, known triggers, acute symptomatic measure . . . the use of [seizure medicine], including the need to monitor for side effects, [and] precautions and reoccurrence risk." Exhibit 11 at 94. After spending one night in the hospital, A.V. returned to her baseline. She was discharged home. Id. at 95-98.

As discussed below, A.V.'s return to baseline, normal EEG, and normal CT are emphasized by the Secretary in contending that A.V.'s initial febrile seizure did not harm A.V. See Resp't's Br. at 38; Oral Arg. Tr. at 13. The perspective of Mr. and Ms. Vinesar is that A.V.'s initial febrile seizure triggered a predisposition to have seizures, which otherwise would not have happened. Pet'rs' Br. at 9-10, Oral Arg. Tr. at 44-45.

A.V.'s response to the vaccination was reported to her pediatrician in an April 24, 2015 appointment. Exhibit 11 at 28. The pediatrician indicated that she would report the incident to drug manufacturers. Id. at 29.[9]

A.V. saw her pediatric neurologist, Dr. Ikramuddin, on May 14, 2015. Exhibit 10 at 62. Dr. Ikramuddin provided an assessment that A.V. was suffering from paroxysmal spells and recommended a follow-up in three months or earlier. Id.

C. Second Seizure[10]

Around July 23, 2015, A.V. had cough and cold symptoms. Exhibit 12-1 at 39; see also Exhibit 11 at 25. A.V. suffered her second seizure on July 26, 2015. Exhibit 12-1 at 23. She tested positive for parainfluenza type 3. Exhibit 12-2 at 99. This date was approximately three months after the previous seizure and A.V. was approximately 10 months old.

When A.V. started seizing, her mother administered Diastat (2.5 mg) with no initial relief. Exhibit 12-1. Emergency services recorded that A.V.'s clothing was then removed to assist with cooling and then A.V. was given Versed (.16 mg) at home and the medication stopped the seizure. Id. Personnel from an emergency medical service recorded that A.V.'s temperature was 100.9 degrees Fahrenheit and transported A.V. to a hospital. Id. at 27. In the hospital, A.V. underwent a series of tests, of which one revealed A.V. was positive for parainfluenza. Exhibit 11 at 25, 92. A.V.'s July 27, 2015 EEG was normal. Exhibit 12-2 at 86. On July 27, 2015, the date A.V. was discharged, the parents were advised to follow up with neurology and were given Diastat for home. Id. at 92.

Dr. Ikramuddin examined A.V. on August 20, 2015. Exhibit 10 at 54-56. Dr. Ikramuddin reported A.V. as having "complex febrile seizure [and] nasty cough." Id. at 56. Dr. Ikramuddin discussed Diastat and the possibility of trial medicine and side effects with Mr. and Ms. Vinesar. Id.

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[9] The Secretary noted that a VAERS report does not appear in the record. Resp't's Br. at 3 n.4. In response, Mr. and Ms. Vinesar did not identify its location. See Pet'rs' Reply.

[10] Mr. and Ms. Vinesar do not provide any details regarding seizures after the first seizure. See Pet'rs' Br. at 2. The lack of details seems consistent with their argument that the only thing that matters is the trigger (alleged to be the vaccine) for the first seizure.

D. Third Seizure

A.V.'s third seizure occurred on November 9, 2015. Exhibit 13 at 12. When the seizure started, Ms. Vinesar administered diazepam rectally, which stopped the seizure. Id. She told EMS personnel that A.V.'s temperature was 99.8 degrees Fahrenheit. Id.

A.V. again went to the hospital. Id. at 12. She tested positive for parainfluenza type 1, but parainfluenza type 3 was not detected. Exhibit 13 at 52. After several hours, A.V. was reported to be "awake, alert, [and] in no acute distress." Id. at 43. Ms. Vinesar told hospital staff that A.V. was "back to baseline and she [wa]s comfortable taking [A.V.] home." Id. Without staying overnight, she was discharged after she returned to her baseline. Id. at 43-44.

E. Fourth Seizure

Another seizure happened approximately one month later. Exhibit 15 at 17 (Dec. 5, 2015). Ms. Vinesar again stopped the seizure by administering diazepam. Id. She reported that A.V.'s temperature was 99.0 degrees Fahrenheit. She was "mentating at baseline." Id. at 21. Although A.V. was brought to the hospital, she was discharged the same day. Id. at 31. Mr. and Mrs. Vinesar were instructed to follow-up with A.V.'s primary care provider within two-to-four days. Id. at 34.

After Mr. and Ms. Vinesar informed A.V.'s pediatrician, Dr. Subramanian, that A.V. had suffered four seizures, he recommended prescription medication. Exhibit 11 at 19 (Dec. 18, 2015). However, the parents preferred herbal therapy. Id. Dr. Subramanian's records indicate that they would "follow with lymphadenopathy if [seizures] persist past 2 weeks." Id. at 20.

F. Events in 2016

In January 2016, because A.V. had experienced four seizures, A.V.'s neurologist, Dr. Shah, recommended an MRI. Exhibit 10 at 49. Dr. Shah further suggested that if febrile seizures reoccurred, "perhaps a 48 hour video EEG may be of value." Id. Mr. and Ms. Vinesar were willing to think about this suggestion. Id.

In 2016, A.V. experienced two more confirmed seizures. The first was on March 1, 2016, when she had a fever (101.3 degrees Fahrenheit) and symptoms consistent with an upper respiratory infection. Exhibit 16 at 16-20. A.V. was transported to the hospital. Id. at 16. The second was on September 12, 2016, and also arose in the context of a low-grade fever. Exhibit 17 at 28. After both the

March 2016 and September 2016 seizures, Dr. Shah saw A.V. Exhibit 10 at 39, 26-30 (noting A.V. saw Dr. Shah on both March 22, 2016 and September 22, 2016). A.V. may have had another seizure on July 19, 2016. See Exhibit 18 at 18. A CT scan from the July 2016 emergency room visit was negative. Exhibit 11 at 82.

After turning two years old, A.V. was brought to her pediatrician for a well-child appointment. Exhibit 11 at 14 (Nov. 4, 2016). She had reached her developmental milestones. Id.

In December 2016, the family brought A.V. to see Dr. O'Connor at the Epilepsy Center. Dr. O'Connor recommended an MRI, a longer EEG, and metabolic studies. Id. at 69 (incomplete record); see also Exhibit 37 at 4 (also an incomplete record for the visit with Dr. O'Connor). Dr. O'Connor also recommended starting antiepileptic ("AEDs") drugs. Exhibit 11 at 69. Dr. O'Connor and the family also discussed that "if the neuroimaging metabolic workup and EEG remain normal and [A.V.] continues to have recurrent seizures, [Dr. O'Connor] would recommend doing some genetic testing specifically looking at sodium channel abnormalities." Id. Dr. O'Connor memorialized the family's response to her recommendations:

> The parents do not want to do any imaging or lab work. [They] do not want to start any medicines. They want to use holistic methods and know a person in their community who treats with multiple holistic medications. As I do not know what these medications/treatments are I am unable to recommend or comment on it.

Id. Dr. O'Connor concluded by stating that "As the family does not want to pursue any of the recommendations I have made, follow up is not needed. . . . They should follow up with . . . Dr. Shah primary neurologist at Lutheran General." Id.

G. Events in 2017, including Genetic Testing

It appears that due to a dispute over whether A.V. should take anti-seizure medication, Dr. Shah declined to continue to treat A.V. Exhibit 10 at 24 (Jan. 16, 2017). The family decided to transfer A.V.'s care to a doctor at the pediatric epilepsy clinic at Lurie Children's Hospital, Sunila O'Connor. Id.

On June 7, 2017, A.V. experienced more seizures for which she went to the emergency room. Exhibit 11 at 66. According to Ms. Vinesar's affidavit, the doctors started her on Keppra. Exhibit 1 (Aff., dated Mar. 21, 2018) ¶ 6. But, Ms.

Vinesar thought Keppra was causing adverse side effects and stopped administering Keppra. Exhibit 20 at 65 (June 23, 2017).

While in Dr. Shah's office on June 23, 2017, A.V. had a prolonged seizure lasting roughly fifteen minutes and was taken to the Advocate's Children's Hospital. Exhibit 10 at 12.[11] A record from this facility stated A.V. "has never been on any [anti-epileptic drug], and has instead been managed on a cocktail of herbal meds that are prescribed by a naturopath which are currently not preventing her seizures." Exhibit 20 at 48. While in the hospital, A.V. was prescribed another medication for preventing seizures, Trileptal. Id. at 66.

Following another seizure, which was on July 1, 2017, Dr. Shah diagnosed A.V. with complex partial epilepsy with generalization. Exhibit 10 at 5. The family planned to see Dr. O'Connor in the next few days. Id. But, a record from a visit with Dr. O'Connor from around this time is not readily apparent.

A.V. had another seizure on August 23, 2017. Exhibit 23 at 20. While at the Advocate Children's Hospital, Ms. Vinesar told a staff member that Mr. Vinesar and she had "weaned her off the Trileptal." Id. They transferred care from Advocate Children's Hospital to the University of Chicago. Exhibit 34 at 3.

Upon a referral from A.V.'s pediatrician, A.V. underwent a 24-hour long-term video EEG on August 24, 2017, at the University of Chicago. Exhibit 11 at 54. The doctor interpreting the EEG, Charles Marcuccilli, determined that it was abnormal. Id. at 55-56. The potential multiple causes included: "structural or vascular abnormalities, toxic, metabolic conditions, hydrocephalus or postictal conditions." Id. at 55.

Dr. Marcuccilli ordered genetic testing. Exhibit 4 at 1. The results, which were reported by Gene Dx on October 24, 2017, are the foundation for the parties' dispute over whether A.V.'s vaccinations in April 2015 harmed her. A.V. possessed *two* SCN1A variants. Exhibit 4 at 2. The more significant variant was c.811_815dupGGCAA. Id. This terminology means five base pairs are duplicated in her DNA. Exhibit A at 2. The duplication, in turn, "creates a premature Stop codon." Exhibit 4 at 3. Because of either "protein truncation or nonsense-mediated mRNA decay," a loss of normal protein function is predicted. Id. Gene Dx stated, "this variant is pathogenic."[12] Id. Overall, according to Gene DX, any

[11] The circumstances by which Dr. Shah continued to treat A.V. are not readily apparent.

[12] The second variant was c.2051 C>T. Exhibit 4 at 2. Gene DX classified this as a "variant of uncertain significance." Id. at 4. Later, other members of A.V.'s family also showed

mutation in an SCN1A gene is associated with "70-80% of Dravet syndrome, 20-24% early-onset cryptic epilepsy, 5-10% GEFS+." Id. at 6 (footnotes omitted).

A.V. saw her pediatrician in September 2017 for a three-year-old well-child appointment. A.V. was taking Keppra. Exhibit 11 at 7. Her development was normal. Id. This normal development, in turn, is a basis for the Vinesar's questions about whether A.V. suffers from Dravet syndrome. See Pet'rs' Br. at 3-4; Pet'rs' Reply at 4. The normal development continued despite abnormalities on EEG and seizures.

H. Events after 2017

After the genetic testing detected the presence of an SCN1A variant, the remaining medical records say relatively little about whether the vaccinations harmed A.V. Thus, they are presented summarily. See Pet'rs' Br. at 3-4; Resp't's Br. at 8-11.

The family returned to the University of Chicago on April 4, 2018. A.V. was taking an antiseizure medication Onfi (clobazam). Exhibit 34 at 389. However, the family believed the medication was causing side effects such as abdominal pain and sleepiness. Rather than maintain pharmacotherapy, the family wanted to initiate a ketogenic diet. Id. at 390. The impression of the neurologist, Dr. Alshaikh, was that A.V. was a three-year old female "with Dravet syndrome (SCN1A mutation)." Id. at 385, 390. Because Ms. Vinesar was questioning the diagnosis, Dr. Alshaikh advised the family to seek a third opinion at Lurie's Children's Hospital. Id. at 390.

In June 2018, Dr. Marcuccilli from the Rush University saw A.V. He obtained information about A.V.'s history of seizures, including that her longest time without a seizure was 39 days. Exhibit 23 (Rush Univ. Ped. Neur.) at 46. Dr. Marcuccilli also reviewed four EEGs. Id. at 48-49. Based upon this information as well as the results of the genetic testing, which he had ordered, Dr. Marcuccilli described A.V. as a "3 year old female with Dravet Syndrome with intractable epilepsy secondary to an SCN1A mutation," and that "her seizure semiology is consistent with Dravet Syndrome given the prolonged seizures." Id. at 49. While A.V. was at risk for developmental delays, her problems were seizures, staring spells, significant drowsiness, and some slurred speech. Exhibit 41 at 46.

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this variant. Exhibit 144; Exhibit 145. Sometimes, Mr. and Ms. Vinesar refer to this variant, instead of the pathogenic variant. See, e.g., Pet'rs' Br. at 3-4.

In June 2018, A.V. had additional genetic testing. Exhibit 39. These results also identified a pathogenic SCN1A gene variant. Id. at 1.

On March 30, 2021, A.V. had a well-child examination when she was six years old. She was being home schooled. Exhibit 147. Ms. Vinesar reported that A.V. is "doing well with learning, speech and development, except she has periods of set back following a seizure episode." Id. at 5.[13]

A November 17, 2021 health summary from Lurie Children's Hospital describes A.V.'s active problems as "Dravet syndrome, intractable, with status epilepticus." Exhibit 148 at 1. She was noted to have a speech problem in February 2020. Id. A.V. was taking antiseizure medication.

It appears that the parties have not attached any significance to more recent medical records. Thus, although those records have been reviewed, they are not further summarized in this decision.

III. Procedural History

Represented by Attorney John McHugh, Mr. and Ms. Vinesar alleged that a series of vaccines given to their daughter, A.V., caused her to suffer a seizure disorder or aggravated a pre-existing problem. Pet., filed Mar. 23, 2018. With the petition, Mr. and Ms. Vinesar submitted a few medical records and an opinion from Marcel Kinsbourne. Exhibits 1-6. Mr. and Ms. Vinesar periodically filed additional medical records.

After the Secretary reviewed this material, the Secretary recommended against an award of compensation. Resp't's Rep., filed Dec. 19, 2018, at 19. As part of his analysis, the Secretary relied upon previous decisions from special masters that found that vaccines do not cause Dravet syndrome, such as Oliver v. Sec'y of Health & Hum. Servs., No. 10-394V, 2017 WL 747846, at *25-26 (Fed. Cl. Spec. Mstr. Feb. 1, 2017) (noting that at least 16 other SCN1A cases had not succeeded), mot. for rev. denied, 133 Fed. Cl. 341 (2017), aff'd, 900 F.3d 1357 (Fed. Cir. 2018). Id. at 10. In light of this history of unsuccessful claims, the Secretary announced that he intended to challenge the reasonable basis for filing the petition. Id. at 11 n.10.

[13] The actual page numbers are not in consecutive order, so this cite is to a page number, automatically generated by CM/ECF.

With the Secretary's report, he also filed an opinion from Dr. Gerald Raymond, who had opined in other SCN1A cases. Dr. Raymond addressed the opinion from Dr. Kinsbourne. Exhibit A. Dr. Raymond discussed the McIntosh article.

Following a status conference to discuss the Secretary's position and evidence, Mr. and Ms. Vinesar were instructed to obtain additional medical records and support. Order, issued Feb. 21, 2019. On successive days, they filed two supplemental reports from Dr. Kinsbourne. Exhibit 45, filed July 24, 2019; Exhibit 46, filed July 25, 2019. In the next status conference, Mr. and Ms. Vinesar expressed an intention to obtain reports from other experts. Order, issued Aug. 9, 2019.

Mr. and Ms. Vinesar did not respond to several orders requesting information regarding their plans for additional expert reports. See Orders, issued Oct. 1, 2019 and Oct. 24, 2019. Consequently, on November 5, 2019, they were directed to show cause why the case should not be dismissed for failure to prosecute. Mr. and Ms. Vinesar addressed that order on December 4, 2019 by submitting a report from Mark McNulty, a statistician. Exhibit 81. A primary purpose of this report was to address the McIntosh article. Mr. and Ms. Vinesar also sought an extension of time to file a report from a third person, Richard Boles. They then filed the report from Dr. Boles. Exhibit 82. Dr. Boles opined that an SCN1A gene did not determine the clinical traits a person would display. Id. at 4. Instead, in the view of Dr. Boles, environmental factors, such as a fever, contribute to the severity of any disorder. Id. at 6-7.

To address the reports from Dr. McNulty and Dr. Boles, the Secretary submitted another report from Dr. Raymond. Exhibit C, filed June 29, 2020. Dr. Raymond opined that the variations in clinical presentation were due to mosaicism, rather than environmental factors. Id. at 4-5. He also touched upon Dr. McNulty's comments regarding the McIntosh article, noting his disagreement with Dr. McNulty's opinion that "McIntosh assumes that all children who developed Dravet syndrome immediately following vaccination would have developed Dravet syndrome even without vaccination…However, it is understood that not all children with SCN1A mutations will develop Dravet syndrome and that a diversity of outcomes is possible." Id. at 10. Dr. Raymond noted that "[i]t is very clear from the understanding of the biology of the variants in SCN1A and the impact on the voltage-gated sodium channel that there is a spectrum of outcomes, but that the severe end of that spectrum when fully expressed in animals, including humans, results in a complex, neurologic presentation that may present with medically

refractory seizures, intellectual disability, ataxia, sleep disturbances, and other manifestations. Id.

On July 1, 2020, the Federal Circuit issued its opinion in Sharpe v. Sec'y of Health & Hum. Servs., 964 F.3d 1072 (Fed. Cir. 2020). As discussed extensively below, the parties differ in how they interpret Sharpe. Mr. and Ms. Vinesar maintain that this case dictates a ruling in their favor. See Pet'rs' Reply, filed Apr. 25, 2022. In contrast, the Secretary contends that it is distinguishable. See Resp't's Response, filed Mar. 25, 2022.

The parties discussed Sharpe in the next status conference, which was held on July 6, 2020. Mr. and Ms. Vinesar were directed to file responsive reports by August 20, 2020. Order, issued July 6, 2020.

Mr. and Ms. Vinesar did not file any reports by the deadline, and they did not seek additional time to comply with the order. But, in the October 7, 2020 status conference, their attorney represented that he had received a report and was gathering the articles cited in the report. Mr. McHugh commented that the Federal Circuit indicated in Sharpe that genetic mutations are factors that create a risk of an adverse reaction in a vulnerable person receiving a vaccine. However, the Secretary's attorney countered that not all genetic mutations are the same and judicial officers had already addressed SCN1A mutations, like the one A.V. suffered.

In the ensuing order, Mr. and Ms. Vinesar were obligated to file an expert report by October 9, 2020, which was the date Mr. McHugh proposed, and any articles by November 6, 2020. Order, issued Oct. 7, 2020. The Secretary, in turn, was directed to file a status report 30 days after Mr. and Ms. Vinesar submitted their expert report. Id.

Over the next six weeks, Mr. and Ms. Vinesar filed multiple articles. See Exhibits 110-121, 124-127. However, they did not submit the report that Mr. McHugh represented he had on hand on October 7, 2020.

Mr. and Ms. Vinesar sought a statement of judicial notice that the diphtheria-tetanus-acellular pertussis vaccine can cause the same adverse effects of a predecessor vaccine, the diphtheria-tetanus-[whole cell] pertussis vaccine. Pet'rs' Mot. for Jud. Notice, filed Nov. 27, 2020. For reasons not explained on the docket, the Secretary did not respond to this motion promptly. Approximately seven months later, Mr. and Ms. Vinesar repeated their arguments and suggested that the case should settle. Pet'rs' Status Rep., filed June 17, 2021.

A comprehensive scheduling order was issued on August 5, 2021. With respect to the opportunity for Mr. and Ms. Vinesar to respond to Dr. Raymond's June 29, 2020 report, the petitioners were ordered to file a status report by August 19, 2021. While Mr. and Ms. Vinesar were instructed that they could still address the report from Dr. Raymond, if they did not respond by August 19, 2021 with a proposed schedule, then they would have been deemed to have determined that they did not want to respond. As to the November 27, 2020 motion for judicial notice, the Secretary was directed to respond by August 26, 2021. Order, issued Aug. 5, 2021.

The August 5, 2021 order also set a schedule to address a motion for an award of attorney's fees and costs on interim basis, which Mr. and Ms. Vinesar had filed on July 12, 2021. The Secretary opposed an award of attorney's fees and costs on the ground that the petitioners had not established the reasonable basis for their claim. Resp't's Resp., filed Aug. 25, 2021. Because the evidence supporting the claim was being developed, an adjudication of the motion for an interim award was deferred. Interim Fees Decision, filed Sept. 14, 2021.

The November 27, 2020 motion for judicial notice was denied because reasonable people could dispute whether the acellular version of the pertussis vaccine causes the same side effects as the whole cell version of the pertussis vaccine. Order, issued Sept. 29, 2021. This same order also reminded Mr. and Ms. Vinesar that their opportunity to respond to Dr. Raymond's June 29, 2020 report was closing.

Following this reminder, Mr. and Ms. Vinesar submitted another report from Dr. Boles. Exhibit 153.[14] In his two-page report, Dr. Boles refers to a 2020 Federal Circuit opinion, although he does not identify the case by name. Dr. Boles concluded that "the SCN1A gene variant confers vulnerability towards disease, not causality for disease. The person carrying the gene variant is vulnerable to injury leading from additional factors, including environmental triggers such as seizures, infection, or vaccination." Exhibit 153 at 2. Dr. Boles also maintained that "the Federal Circuit has reached the conclusion that I had urged in my [previous] report." Id.

In a December 10, 2021 status conference, Mr. McHugh confirmed that Dr. Boles had read Sharpe. When asked whether the Secretary wanted Dr. Raymond

[14] Mr. and Ms. Vinesar first attempted to file this report from Dr. Boles on October 27, 2021. CM/ECF 114. However, due to various deficiencies, they did not actually file the report until December 23, 2021.

to respond to Dr. Boles's recent report, the Secretary declined. The Secretary suggested that the case could be resolved on the papers.

Mr. and Ms. Vinesar argued that the evidence in the record supported a ruling that they are entitled to compensation. Pet'rs' Mot. for Judgment, filed Jan. 12, 2022. This pending motion is eleven pages. This motion could be construed to raise both a causation-in-fact and significant aggravation claim. The next day, an order regarding the anticipated scope of briefs was issued. Order, issued Jan. 13, 2022. While that January 13, 2022 order arguably expanded the topics beyond those which Mr. and Ms. Vinesar discussed in their motion, they declined to submit a supplemental brief. See Order, issued Jan. 27, 2022.

The Secretary sought a decision that the petitioners are not entitled to compensation. Resp't's Resp. to Pet'rs' Mot. for Judgment, filed Mar. 25, 2022. With this response, the Secretary filed another report from Dr. Raymond. Exhibit D.

Mr. and Ms. Vinesar replied on April 25, 2022. The parties' briefs raised several questions. Thus, an oral argument was held on January 18, 2023. With the completion of oral argument, the case is ready for adjudication.

IV. Standards for Adjudication

Petitioners are required to establish their case by a preponderance of the evidence. 42 U.S.C. § 300aa–13(1)(a). The preponderance of the evidence standard requires a "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010) (citations omitted). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between "preponderant evidence" and "medical certainty" is important because a special master should not impose an evidentiary burden that is too high. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing special master's decision that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357 (Fed. Cir. 2000); Hodges v. Sec'y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with dissenting judge's contention that the special master confused preponderance of the evidence with medical certainty).

Whether petitioners have presented preponderant evidence is evaluated, below, in two separate parts. Section V first examines whether Mr. and Ms. Vinesar have met their burden of showing either that a vaccination was the cause-in-fact of A.V.'s seizure disorder or a vaccination significantly aggravated A.V.'s seizure disorder. Section VI then examines whether the evidence preponderates in favor of finding that A.V.'s genetic mutation caused her seizure disorder.

V. Analysis Part 1: Whether Mr. and Ms. Vinesar Have Met Their Burden of Proof to Show a Vaccination Either was the Cause-in-Fact of A.V.'s Seizure Disorder Or Significantly Aggravated A.V.'s Seizure Disorder

Whether Mr. and Ms. Vinesar are asserting *only* a causation-in-fact claim, *only* a significant aggravation claim, or a causation-in-fact claim *and* a significant aggravation claim is not clear. See Pet'rs' Br. at 4, 9-10. In such circumstance, the analysis can follow the elements for a significant aggravation claim.

As confirmed in W.C. v. Sec'y of Health & Human Servs., 704 F.3d 1352, 1357 (Fed. Cir. 2013), the elements of an off-Table significant aggravation case were stated in Loving v. Sec'y of Health & Hum. Servs., 86 Fed. Cl. 135, 144 (2009). There, the Court blended the test from Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1279 (Fed. Cir. 2005), which defines off-Table causation cases, with a test from Whitecotton v. Sec'y of Health & Human Servs., 81 F.3d 1099, 1107 (Fed. Cir. 1996), which concerns on-Table significant aggravation cases. The resulting test has six components. These are:

> (1) the person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a "significant aggravation" of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significantly worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving, 86 Fed. Cl. at 144.

In resolving claims of significant aggravation, special masters may focus their analysis on the last three prongs of the Loving test, which correspond to the traditional Althen factors. Walker v. Sec'y of Health & Hum. Servs., No. 18-299V, 2022 WL 11141194, at *3 (Fed. Cl. Spec. Mstr. Sep. 27, 2022) (citing Hennessey v. Sec'y of Health & Hum. Servs., No. 01-190V, 2009 WL 1709053, at *42 (Fed. Cl. Spec. Mstr. May 29, 2009), mot. for rev. denied, 91 Fed. Cl. 126 (2010)).

A. Althen Prong One / Loving Prong Four – A Medical Theory

The oral argument clarified the parties' respective positions. Mr. and Ms. Vinesar are putting forth one theory to explain how the vaccines could have harmed A.V. This theory contains two steps: 1) a vaccine can cause a fever, and a fever can cause a seizure and 2) the first febrile seizure causes the later seizures. Tr. at 54-55, 61.[15]

The Secretary's opposition focuses on the second step. Through Dr. Raymond, the Secretary concedes that a vaccine can trigger a febrile seizure. Oral Arg. Tr. at 12-13; Resp't's Br. at 32, citing Exhibit D (Dr. Raymond's report). Dr. Raymond's concession regarding the first febrile seizure is consistent with his previous testimony. Oral Arg. Tr. at 13; Exhibit A at 2. However, the Secretary and Dr. Raymond maintain that the first febrile seizure did not cause A.V.'s seizure disorder. Oral Arg. Tr. at 13; Exhibit D at 3.

A first seizure differs from a seizure *disorder*. See Stone, 676 F.3d 1373 (citing 2011 WL 836992 at *4); see also Holmes v. Sec'y of Health & Hum. Servs., No. 08-185V, 2011 WL 2600612 at *11 (Fed. Cl. Spec. Mstr. Apr. 26, 2011), mot. for rev. denied, 115 Fed. Cl. 469 (2014); Deribeaux, 105 Fed. Cl. at 594. In some cases, including A.V.'s, the first seizure does not cause any lasting harm. Moreover, a seizure that resolves in approximately one day or two days without any sequellae would not fit the Vaccine Program's severity rule. 42 U.S.C. § 300aa–11(c)(1)(D); Oral Arg. Tr. at 18. Thus, to receive compensation, the

[15] The Vinesars did not advance a theory based on cytokines. Pet'rs' Br. Nevertheless, the Secretary argued that this theory is not persuasive. Resp't's Br. at 37 (citing cases). The Vinesars also did not present a theory based on cytokines in their April 25, 2022 Reply. When asked to explain their theory in oral argument, the Vinesars did not refer to a theory based on cytokines. See Oral Arg. Tr. at 10-11. Under these circumstances, discussion of a cytokine-based theory is not required.

Vinesars must claim (and have claimed) that the vaccination contributed to A.V.'s seizure disorder.

In terms of vaccines and a generic (meaning non-genetic) seizure disorder, the Vinesars have not presented strong evidence. They have emphasized a set of three articles plus an abstract, of which all involve the DTaP vaccine, to support their claim that the DTaP vaccine causes seizures. Pet'rs' Br. at 5-7, Oral Arg. Tr. at 11. They have also cited an article about the whole-cell version of the pertussis vaccine. However, these articles do not link the acellular pertussis vaccine to a seizure disorder. They are taken up in chronological order, starting with the earliest.

The earliest published article is the only one of this set of articles that focuses on the whole cell version of the pertussis vaccine. Bellman MH et al., Infantile spasms and pertussis immunization, 8332 Lancet 1031 (1983). However, the Vinesars did not actually file this article as an exhibit. Moreover, neither Dr. Kinsbourne nor Dr. Boles cited Bellman in their reports. See Exhibits 2, 45, 46, 82, 114, 153. Because it is not an exhibit, additional discussion is not necessary. Sheller Est. of Sheller v. Sec'y of Health & Hum. Servs., No. 18-696V, 2022 WL 4075946, at *7 (Fed. Cl. Spec. Mstr. Aug. 15, 2022), mot. for rev. denied, 164 Fed. Cl. 398 (2023), appeal docketed, No. 23-1746 (Fed. Cir. Apr. 12, 2023). Regardless, Bellman considers the incidence of infantile spasms after the whole-cell version of pertussis vaccines. See Exhibit D at 2. The Vinesars have not presented any persuasive reason to extend Bellman to a different vaccine (the acellular form of pertussis vaccines) and to a different condition (epilepsy). See Resp't's Br. at 33-34 (citing cases declining to rely upon Bellman). While the Vinesars cannot find support in Bellman primarily because Bellman is not an exhibit, the Vinesars did at least file the three other articles and one abstract.

In 1999, Dennis A. Conrad and Hal B. Jenson compared the whole-cell version of pertussis vaccines and the acellular version of pertussis vaccines.[16] The authors assembled data from several sources, including the Centers for Disease Control and Prevention and the American Academy of Pediatrics Committee on Infectious Disease. For children who received the acellular pertussis vaccine, the

[16] The Vinesars filed this article without bibliographic information. It appears that the appropriate citation is Dennis Conrad & Hal Jenson, "Using Acellular Pertussis Vaccines for Childhood Immunization. Potential Benefits Far Outweigh Potential Risks," 105 Postgrad Med. 165 (1995). See Kottenstette v. Sec'y of Health & Hum. Servs., No. 15-1016V, 2020 WL 3579995, at *2 n.2 (Fed. Cl. Spec. Mstr. June 2, 2020), mot. for rev. denied, 2020 WL 4592590 (Fed. Cl. July 27, 2020), reversed, 861 Fed. App'x. 433 (Fed. Cir. 2021).

authors commented: "the number of subjects . . . has been too small to calculate the risk of extremely rare but potentially life-threatening reactions (eg, immediate anaphylaxis, encephalopathy)." Exhibit 138 at pdf 5.[17] Nevertheless, they concluded "DTaP vaccines do and will continue to cause undesirable effects, albeit at reduced frequency and severity compared with whole-cell vaccines." Id. at pdf 7.

In 2000, a set of researchers from the United States government used the VAERS database to compare adverse events following the whole-cell version of pertussis vaccines with adverse events following the acellular version of pertussis vaccines. Exhibit 139.[18] M. Miles Braun and colleagues found that the acellular version was at least as safe as the prior version. Id. With respect to seizures or convulsions, the researchers examined 34 VAERS reports. Id. at 4. (Although the text is not clear about which type of vaccine preceded the seizures or conclusions, it appears that the relevant VAERS reports concern the acellular pertussis vaccine.) Of this group, "none of the 34 were reported to have developed a seizure disorder or epilepsy." Id.

The third exhibit comes from 2002.[19] Exhibit 140. The Vinesars filed the abstract, not the entire article. The abstract does not provide any information about whether children who received the acellular pertussis vaccines experienced a seizure disorder. See id.

In 2003, Nicole Le Saux and colleagues compared, among other points, the frequency of seizures after the earlier whole-cell version of a pertussis vaccine with the frequency of seizures after the modern acellular version of a pertussis

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[17] It appears that the Vinesars incorrectly labeled the Conrad article as exhibit number 32. The Vinesars' exhibit list, filed on December 23, 2021, reflects that this article is exhibit 138. Since exhibit 32 is already associated with medical records, the Conrad article will be cited as exhibit 138. The Vinesars submitted this article in manuscript form. Therefore, the page cites are to the pdf version, rather than the version that appears in printed journals.

[18] It appears that the Vinesars incorrectly labeled the Braun article as exhibit number 33. The Vinesars' exhibit list, filed on December 23, 2021, reflects that this article is exhibit 139. Since exhibit 33 is already associated with medical records, the Braun article will be cited as exhibit 139.

[19] The Vinesars also filed this article without any bibliographic information. However, their brief provides the following: LA Jackson et al., "Retrospective population-based assessment of medically-attended injection site reactions, seizures, allergic responses and febrile episodes after acellular pertussis vaccine combined with diphtheria and tetanus toxoids," 21 The Pediatric Infectious Disease Journal 781 (2002).

vaccine in Canadian hospitals. They found "a 79% decrease in febrile seizures associated with receipt of [acellular] pertussis vaccine." Exhibit 137 at e348 (Le Saux et al.). This finding supports the first aspect of the Vinesars' theory: that vaccines can cause a fever and a fever can cause a seizure. The problem is that Le Saux and colleagues report only about hospitalizations for the febrile seizure. They do not report about any long-term consequences. See id. Thus, Le Saux does not meaningfully contribute to analyzing whether an initial febrile seizure can cause other seizures.

Against these three articles and one abstract, the Secretary and Dr. Raymond point to a 2010 paper by Wan-Ting Huang and others, including people from the Centers for Disease Control and Prevention. Exhibit D at 3, citing Exhibit D-2; see also Resp't's Br. at 33-34. In this article, researchers accessed information contained by managed health organizations and kept in the Vaccine Safety Datalink. Exhibit D-2 at e264 (Huang). The researchers identified nearly one-half million children (433,654) who received the DTaP vaccine. Id. at e265. After searching medical records for various diagnostic codes, the researchers determined that 5,205 patients had 7,191 seizure events. Id. The researchers used two methods to analyze whether the DTaP vaccine was associated with an increased incidence of seizures within four days of the vaccination: the risk-interval cohort method and the self-controlled case series. Id. The authors concluded: "Our study did not observe a significantly increased risk of seizures within 0 to 3 days after DTaP vaccination." Id. at e266. The increased relative risk was below 1.0. Id. at e267, Table 2 (risk interval cohort analysis) and Table 3 (self-controlled case series). This study did not address whether children who received a DTaP vaccine had a greater incidence of seizure disorders. However, any decline in seizures would seem to mean a decline in seizure disorders.

In short, the collection of evidence the Vinesars submitted (three older articles plus an older abstract) does not persuasively support the Vinesars' theory that DTaP vaccines can cause a seizure disorder. The Vinesars seem to assume that proving a vaccine causes a seizure is the same as proving a vaccine causes a seizure *disorder*. For example, the Vinesars do not argue that a febrile seizure can lower a person's seizure threshold. See Pet'rs' Br. The Vinesars have not advanced that argument despite Dr. Kinsbourne's assertion that the younger a child experiences a first febrile seizure, the greater likelihood of developing epilepsy. Exhibit 45 at 7-8, citing Berg and Van Stuijvenberg. The absence of this argument is construed as a waiver of any argument based upon that evidence. See Vaccine Rule 8(f).

If the only question were "have the Vinesars established, by a preponderance of evidence, that DTaP vaccines can cause a seizure disorder?," the answer to that question would be "no." For the reasons explained above, evidence connecting the acellular form of pertussis vaccines to a seizure disorder is lacking. Under this understanding, the Vinesars have not met their burden of proof regarding Althen prong one.

However, the question might be recast as asking whether preponderant evidence shows that DTaP vaccines can cause (or significantly aggravate) a seizure disorder in a child with an SCN1A mutation. Because this version implicates a factor (the mutation) unrelated to the DTaP vaccination as the cause of A.V.'s seizure disorder, this analysis is separated and can be found in section VI.C. below.

B. Althen Prong Two / Loving Prong Five – A Logical Sequence of Cause and Effect

Just as the definition of the condition for which the Vinesars are seeking compensation affects the determination on Althen prong one (or Loving prong four), a distinction between a seizure and a seizure disorder (epilepsy) influences the analysis of Althen prong two (or Loving prong five). To repeat, the Vinesars are not seeking compensation for the immediate effects A.V. suffered from her April 2015 seizure. These immediate effects dissipated within a few days. Exhibit 11 at 94-98 (noting A.V. had returned to her baseline and discharging her from the hospital). As such, the Vinesars cannot receive compensation for this transient, although frightening, incident. See 42 U.S.C. § 300aa–11(c)(1)(D); Barclay v. Sec'y of Health & Hum. Servs., 122 Fed. Cl. 189, 198 (2015); Santini v. Sec'y of Health & Hum. Servs., No. 06-725V, 2014 WL 7891507, at *19 (Fed. Cl. Spec. Mstr. Dec. 15, 2014), mot. for rev. denied, 122 Fed. Cl. 102, 109 n.12 (2015). Thus, the abundant evidence that the DTaP vaccine triggered A.V.'s first seizure is beside the point.[20]

The actual issue is whether the DTaP vaccination triggered (or caused or significantly aggravated) A.V.'s epilepsy. On this critical question, the Vinesars have not identified any treating doctor who indicated that the vaccination caused any lasting harm to A.V. Oral Arg. Tr. at 38; see also Pet'rs' Br. at 9 (discussion of prong two consisting of an (accurate) assertion that a doctor who treated A.V.

[20] An example of evidence showing that the DTaP vaccine caused her fever is the report when A.V. was first admitted to the hospital in April 2015. Exhibit 3-1 at 36-37. The Secretary does not dispute this evidence. Resp't's Br. at 38.

during her first hospitalization attributing her fever to the vaccine), Pet'rs' Reply at 2 (similar).

The Secretary emphasizes that the Vinesars have not established that the April 20, 2015 seizure caused "any lasting injury." Resp't's Br. at 38. In support, the Secretary points to a normal EEG and a normal CT scan. Exhibit 3-2 at 75-76. By the time of A.V.'s discharge, she appeared normal. This information, in turn, is the evidentiary foundation for Dr. Raymond's assertion that "there was no evidence of altered mental status or other evidence of encephalopathy." Exhibit C at 2.

The Vinesars have not countered the contention that A.V. returned to her baseline shortly after her April 20, 2015 seizure. Their reply brief ends its discussion regarding events in A.V.'s life with the febrile seizure. See Pet'rs' Reply at 2. The Vinesars do not discuss the normal EEG and the normal CT scan. See id. So, too, the reports from the Vinesars' experts are relatively quiet on this topic. For example, while Dr. Kinsbourne acknowledged the normal EEG and CT scan (Exhibit 45 at 2), he does not explain how these results fit with his theory that the febrile seizure harmed A.V. Dr. Boles also recognized A.V.'s normal EEG and CT scan in his first report. Exhibit 82 at 2. Yet, in a later report, Dr. Boles states that the "vaccination was the environmental trigger for brain injury." Exhibit 153 at 2. However, Dr. Boles cites no evidence of brain injury (other than the seizure).

To the extent that Dr. Boles's opinion assumes that the first febrile seizure injured A.V.'s brain, then this case is analogous to Stone. There, Dr. Kinsbourne maintained that a vaccine-induced complex febrile seizure harmed the child. 2010 WL 1848220 at *2. But, in Dr. Kinsbourne's testimony, he could not point to any clinical manifestation of the brain damage that he asserted occurred. Id. at *36. In response, Dr. Raymond acknowledged that complex febrile seizures could injure the brain, but "'we have no evidence that the complex febrile seizures actually injure the brain.'" Id., quoting the transcript. Thus, the chief special master found: "There is simply no evidence that Amelia's initial seizure caused any brain damage." Id. at *38. When the case reached the Federal Circuit, the Federal Circuit summarized that a "key component of Dr. Kinsbourne's theory is that the initial seizure caused some form of lasting brain injury that had downstream consequences for both children, specifically a lower seizure threshold." Stone, 676 F.3d at 1384. The Federal Circuit reviewed the evidence discussed above and found the chief special master's analysis was not erroneous. The chief special master could find that "Dr. Kinsbourne's inference of brain damage, in the face of clinical records showing no brain damage, was unpersuasive." Id. at 1385.

Just as in Stone, the evidence that the first febrile seizure harmed A.V. is lacking. A.V. had a normal EEG, a normal CT scan, and was discharged a day after her seizure. In a follow-up appointment, A.V.'s pediatric neurologist did not seem particularly worried and recommended the next appointment occur in three months or earlier. Exhibit 10 at 65. A.V. did not have her second seizure until approximately three months after the first seizure and that second seizure occurred in the context of a parainfluenza infection. Exhibit 11 at 25.

In addition to the lack of clinical manifestations of the harm potentially caused by the first febrile seizure, another cause has been proposed. After A.V.'s genetic mutation was discovered, a treating doctor associated her condition with the genetic mutation. Exhibit 23 (Rush Univ. Ped. Neur.) at 49 (describing A.V. as a "3 year old female with Dravet Syndrome with intractable epilepsy *secondary* to an SCN1A mutation") (emphasis added).

Accordingly, the Vinesars have not established with preponderant evidence that the DTaP vaccine caused or worsened A.V.'s seizure disorder. They have not met their burden of proof regarding Althen prong two / Loving prong five.

C. Althen Prong Three / Loving Prong Six -- Timing

A striking aspect about the chronology of events in A.V.'s case is that she experienced her first febrile seizure about thirteen hours after vaccination. See Exhibit 11 at 30 (time of vaccination), Exhibit 3-2 at 80-81 (time of seizure). While this short latency is notable, an interval of less than one day between the vaccination and the first seizure in children with an SCN1A mutation is common. See Oliver, 2017 WL 747846, at *4; Snyder, 2011 WL 3022544, at *2; Deribeaux, 2011 WL 6935504, at *3; Hammitt, 2010 WL 3735705, at *2; Stone, 2010 WL 1848220, at *2-3. Yet, in all these cases, the Federal Circuit ultimately found that the special master was not arbitrary in not awarding compensation. The denial of compensation was based, in whole or in part, on a finding that the Secretary had established with preponderant evidence that the SCN1A mutation caused the child's seizure disorder. That critical question is discussed as the second part of the analysis in section VI.

D. Synopsis Regarding Petitioners' Burden

Regardless of whether Mr. and Ms. Vinesar are proceeding under an off-Table causation-in-fact case or an off-Table significant aggravation case, they bear a burden of proof for two critical aspects. Here, first, they have not met their burden to present a medical theory to explain how an acellular pertussis vaccine

can harm a recipient, either by causing a seizure disorder or by aggravating a seizure disorder. Mr. and Ms. Vinesar have focused much (if not all) their attention on whether a vaccination might lead to a febrile seizure. But, proof of an isolated febrile seizure differs from proof regarding a seizure disorder. Mr. and Ms. Vinesar have not persuasively explained any mechanism by which a vaccination might cause a seizure disorder. This lack of persuasive evidence means that Mr. and Ms. Vinesar cannot prevail on Althen prong one / Loving prong four. Without proof on this element, Mr. and Ms. Vinesar cannot receive compensation.

Second, Mr. and Ms. Vinesar also have not met their burden of showing the vaccination was the logical reason for either the development of the seizure disorder or worsening of A.V.'s seizure disorder. The evidence does not preponderate in favor of finding that the April 20, 2015 vaccination caused any lasting harm. The EEG and CT were normal, and the hospital doctors discharged A.V. the next day. This evidence points away from implicating the vaccination as causing a lasting harm.

For these reasons, Mr. and Ms. Vinesar have failed to meet their burden of proof regarding Althen prong one (corresponding to Loving prong four) and Althen prong two (corresponding to Loving prong five).[21] Without this showing, the burden of proof has not shifted to the Secretary. LaLonde v. Sec'y of Health & Hum. Servs., 746 F.3d 1334, 1340 (Fed. Cir. 2014).

VI. Analysis Part Two – Did the Secretary Meet His Burden to Establish a Factor Unrelated to the Vaccinations Caused (or Worsened) A.V.'s Seizure Disorder

If for the sake of argument it were assumed that Mr. and Ms. Vinesar had met their burden of proof, then the Secretary may show A.V.'s "condition . . . is due to factors unrelated to the administration of the vaccine." 42 U.S.C. § 300aa–13(1)(B). "If a petitioner successfully satisfies the Loving inquiry, the burden shifts to the government to prove by a preponderance of the evidence that a 'factor unrelated' to the vaccine caused the petitioner's injuries." Sharpe, 964 F.3d at 1080.

[21] The analysis of Althen prong two / Loving prong five does not consider whether the SCN1A genetic mutation provides "compelling evidence of a different cause for the injury." Stone, 676 F.3d at 1380. The genetics issue is discussed in section VI.A. below.

Here, the Secretary through Dr. Raymond has identified A.V.'s genetic mutation as the cause of her seizure disorder. Exhibit D at 3; Exhibit A at 6. To understand this claim, basic information about genes is provided in section VI. A. Then, three types of evidence (animal models, information about A.V.'s genetic mutation, and human studies) are discussed in section B, section C, and section D, respectively. Then, the leading cases---including cases involving an SCN1A mutation---are again examined in section E.

A. Genes

Previous decisions have set forth foundational, if complicated, information about genes and why genetic mutations cause a disease. See Snyder, No. 7-59V, 2011 WL 3022544, *13-15 (Fed. Cl. Spec. Mstr. May 27, 2011); Oliver, No. 10-394V, 2017 WL 747846, at *7-9, *20; Deribeaux, No. 05-306V, 2011 WL 6935504, at *7–9. Genes contain segments of DNA. Through a process involving RNA, the gene provides instructions for cells to assemble sequences of amino acids into proteins. Exhibit A at 2.

The relevant protein here is a sodium channel. The sodium channel controls the flow of sodium molecules across a neuron's cell membrane. Exhibit A at 3. To be more detailed, when less sodium than expected is conducted, certain neurons that inhibit excitation are not activated, resulting in over-excitement. Exhibit 82 at 5; Exhibit 45 at 4; Exhibit A at 3.

In general, mutations in SCN1A genes are associated with different neurological conditions, such as Dravet syndrome, which is also known as severe myoclonic epilepsy in infancy ("SMEI"); generalized epilepsy with febrile seizures plus ("GEFS+"); other types of epilepsy; and migraines. Exhibit A at 3, Exhibit 82 at 3.

The parties and their experts differ in their interpretation about the variation in conditions.[22] For Dr. Kinsbourne and Dr. Boles, the range of potential outcomes in people with SCN1A mutations means that genes do not tell the whole story. Something else, an environmental factor (such as an infection or a vaccination), can modify or worsen a person's outcome. See Exhibit 45 (Dr. Kinsbourne's report) at 5-10, Exhibit 82 (Dr. Boles) at 6-8. In contrast, Dr. Raymond states that

[22] The experts and medical literature sometimes use the term "phenotype." Phenotype means "the observable morphologic, biologic, and physiologic characteristics of an individual, either in whole or with respect to a single or a few traits, as determined by a combination of the genotype and the environment." Dorland's Illus. Med. Dictionary (33 ed. 2012) at 1410.

the variability in outcome is more readily explained by differences in the genetic mutation. See Exhibit C at 4.

Dr. Raymond asserts that "More recent papers… have demonstrated an increase in predictability." Exhibit C at 5. For example, Dr. Raymond stated mosaicism can explain apparently disparate outcomes. Id. at 4, citing Francesco Nicita et al. (Exhibit C-7). Dr. Boles did not respond to Dr. Raymond's discussion of mosaicism or predictability. See Exhibit 153; Oral Arg. Tr. at 41.

Thus, the crux of this issue could be viewed as whether the evidence preponderates in favor of finding a genetic mutation in an SCN1A gene either (1) constitutes a predisposition toward a disease or (2) constitutes a cause sufficient by itself to cause disease.

Four sources support a finding that A.V's SCN1A mutation is likely to be the sole cause of her epilepsy. The first three are evidentiary – articles about animal models, articles about the genetic mutations, and articles about developmental delays in children with SCN1A disorders.[23] The fourth category consists of prior adjudications.

B. Animal Models

In his first report, Dr. Raymond put forward two animal models for Dravet syndrome. The first animal model is used by researchers in the Catterall group. See Exhibit A at 3-4 (citing, among others, an article by Oakley and an article by Yu). Another mouse model was used by Ito. Exhibit A-15.

In response, Dr. Kinsbourne did not challenge the usefulness of the Catterall group's mouse model. See Exhibit 45. Dr. Kinsbourne endorsed articles using a different animal model. Exhibit 45 at 8, citing Dutton et al. (Exhibit 58). The same is true for Dr. Boles. He did not criticize the Catterall model. See Exhibit 82. Dr. Boles also relied upon Dutton and an extension of that work by Salgueiro-Pereira. Exhibit 82 at 7-8.

[23] The parties have filed an abundance of articles about SCN1A mutations, which have been reviewed. The Vinesars did not discuss any article about SCN1A mutations in their briefs. However, the Secretary has an extensive discussion. Furthermore, the parties were asked to identify the articles that were most helpful to their positions and the parties identified those supporting articles at oral argument. Oral Arg. Tr. at 58-61. Thus, this decision focuses on the most important articles in the record.

Thus, a preponderance of evidence supports analogizing the human condition of Dravet syndrome to the mouse models used by the Catterall group in Oakley and Yu. See also Exhibit 48 at 81 (Auvin); Snyder, No. 7-59V, 2011 WL 3022544, at *32-33. Of these two articles, Yu carries more weight.

Yu, which was published in 2006, reports on two experiments in mice. In one set of mice, researchers created mice in which both SCN1A genes were knocked out. In other words, these mice were homozygotes. These mice died within eighteen days of being born. Exhibit A-11 at 1143 (Yu). What happened with the other mice matches more closely with what could be happening in humans. In mice with only one SCN1A gene knocked out (meaning the mice were heterozygotes), they "first showed recurring behavioral seizures and sporadic deaths during the weaning period between P21 and P27." Id. at 1144. "The seizures were spontaneous." Id.

In Oakley, which was published in 2009, the researchers continued working with heterozygous mice. (Yu is reference 14 in Oakley.) This article begins: "Heterozygous loss-of-function mutations in the… sodium channel cause severe myoclonic epilepsy in infancy (SMEI)." Exhibit A-9 at 3994. (Oakley et al.). In discussing the manifestations of SMEI in humans, the researchers stated: "A crucial feature of human SMEI is increasing severity of seizures with age." Id. at 3995. "Infants with SMEI frequently have febrile seizures before developing spontaneous seizures. This suggests a developmentally regulated seizure susceptibility in which initial seizures are usually realized only with an additional provoking factor such as elevated temperature." Id. at 3996.

The researchers "tested susceptibility to temperature-induced seizures for 3 age groups." Id. at 3995. They found that increases in temperature could provoke a seizure. With respect to the different days, the researchers connected the age of vulnerability to temperature-induced seizures to an age when a sodium channel found in prenatal and early postnatal development ($Na_v1.1$) is replaced with the mature sodium channel ($Na_v1.3$). Id. at 3998.

Collectively, Yu and Oakley demonstrate that mice lacking one SCN1A gene will have seizures spontaneously at a certain age. If the mice are heated (an increase in temperature serving as a proxy for a fever), then the mice can have seizures earlier than they would have in the absence of the heating. While Dr. Raymond cited these articles in his first report, neither Dr. Kinsbourne nor Dr. Boles contested the points of the articles. See Exhibits 45 and 82. Rather, they rely upon different animal models.

The set of animal models on which Dr. Kinsbourne and Dr. Boles rely were used in two experiments led by Andrew Escayg. See Exhibit 45 at 8 and Exhibit 82 at 7-8. The lead authors for the two studies are Stacey Dutton and Ana Rita Salgueiro-Pereira.

The genetic mutation of these mice (R1648H) causes human children to develop GEFS+. Exhibit 45 at 8; Exhibit C at 7; see also Exhibit 82 at 7 (asserting this mutation could lead to SMEI or GEFS+). Thus, Dr. Raymond challenges the usefulness of this model. Exhibit C at 7-8. In Dr. Raymond's view, experiments with this model do "not recapitulate the features of [Dravet syndrome]." Id. at 7. He also notes that this mutation was not the mutation in A.V. Id. at 8.

In support of the difference with R1648H mice, Dr. Raymond cited a 2010 article by Martin. Exhibit C at 7. These researchers found that among fourteen mice with a heterozygous mutation, two mice experienced seizures spontaneously. Exhibit C-22 at 9827 (Martin et al.). The authors indicated that the low frequency of seizures "is likely due, in part, to the mixed genetic background and is consistent with the variability observed among affected members of GEFS+ families." Id.[24] Dr. Raymond also asserted that the R1648H model has "none of the other associated features reported of [Dravet syndrome] phenotype." Exhibit C at 7.

On these points, Dr. Raymond's criticisms miss their mark. It appears that Dr. Raymond is requiring a high level of similarity. For example, although he may accurately state A.V. does not possess a R1648H mutation, Dr. Raymond has not shown that the *Scn1a* knockout model used in the Yu and Oakley experiments is the same as A.V.'s mutation. Further, as Dr. Kinsbourne comments, Dravet syndrome and GEFS+ are on a spectrum and A.V has not experienced the developmental delays of Dravet syndrome. Exhibit 45 at 13. However, as discussed below, Dr. Raymond has an additional criticism of the Escayg group, which is more on target.

The earlier of the two papers from the Escayg group is by Dutton. The purpose of the experiments about which Dutton reported was to determine whether early-life febrile seizures lead to more severe epilepsies. Exhibit 58 at 159. The researchers conducted two experiments of which both involved RH heterozygous mice and wild-type littermates. Id. at 160.

[24] Citing Yu (reference 15), the researchers also stated that spontaneous seizures were detected in 3 of 7 *Scn1a*$^{+/-}$ mice.

The first paradigm ("prolonged febrile event") involved heating the mice gradually and maintaining an elevated body temperature for thirty minutes. The researchers counted the seizures and rated the severity of the seizures. Id. In the second paradigm ("acute/prolonged febrile event"), the researchers on the first day gradually elevated the mice's temperature until a seizure occurred. On the second day, the researchers again gradually increased the temperature but then maintained the high temperature for thirty minutes. The researchers again counted and scored the seizures. Id.

Two months later, the researchers gave the groups of mice that were heated plus mice that were not heated a drug to induce a seizure. The researchers then tested the mice in a variety of ways. The mice that were not heated experienced fewer seizures and the seizures were of less severity compared with the A/PFE mice. Id. at 164 (table 2). The researchers summarized their conclusion: "early life [febrile seizures] resulted in lower latencies to induced seizures, increased severity of spontaneous seizures, hyperactivity, and impairments in social behavior and recognition memory during adulthood." Id. at 159 (abstract). Based upon their conclusions, the researchers recommended pharmacological intervention to prevent febrile seizures in patients with SCN1A mutations. Id. at 169.

The lead author for the second article from the Escayg group relevant here is Ana Rita Salgueiro-Pereira. In the introduction, the authors begin: "SCN1A ($Na_v1.1$ sodium channel) mutations cause Dravet syndrome (DS) and GEFS+ (which is in general milder)." Exhibit C-21 at 31 (abstract). Citing the Dutton article, these researchers indicated that "hyperthermic long seizures/*status epilepticus* can worsen the mild phenotype of *Scn1a* knock-in mice carrying the R1648H mutation ($Scn1a^{RH/+}$)." Id. at 32.

The researchers divided mice into six categories: wild-type, heterozygous mutant, wild-type that had seizures induced by temperature, heterozygous mutant that had seizures induced by temperature, wild-type which had seizures induced by a drug, and heterozygous mutants that had seizures induced by a drug. Id. at 32. For the temperature-induced seizure group and the drug-induced seizure group, the mice experienced a seizure once per day for ten days. Id. The researchers found the mice with hyperthermia-induced seizures developed long-lasting epilepsy and long-lasting dysfunction in behavior and cognition. Id. at 34. The researchers concluded that "Our results are not consistent with the concept of [Dravet syndrome] as pure channelopathy." Id. at 41.

Dr. Raymond criticized Dr. Kinsbourne's reliance on this paper because A.V "did not have an initial prolonged seizure or a train of daily seizures as the mouse

model in the experiments of Salgueiro-Pereira et al. were exposed to." Exhibit C at 8. Dr. Boles did not answer this criticism, leaving Dr. Raymond's point unrebutted. See Exhibit 147.

C. Factors about the Genetic Mutation in A.V.

GeneDx reported a frameshift in exon 6 of the SCN1A gene. Exhibit 4 at 3. GeneDx also recommended more testing and when the Vinesars were tested, this genetic mutation was only found in A.V and was not present in other family members. Id. at 4; see also Exhibit D at 1. The parties agreed that a mutation arising *de novo* is more likely to cause a disease. See Oral Arg. Tr. at 41-45; see also Exhibit 82 at 3.

This genetic mutation prevents the entire protein from forming, due to a premature stop codon. Without a full structure, A.V. will have a loss of function. Exhibit C at 2. Dr. Boles does not dispute that A.V.'s body system will not assemble the entire protein. Instead, he asserts "Loss-of-function (LOF) SCN1A mutations can be associated with very different outcomes, and are not exceptions to the fact that the SCN1A mutation alone does not confer destiny on the individual." Exhibit 82 at 5. In support, he cites three articles.

Of these three articles, Jiang supports the Vinesars' claim the most. Jiang, which was published in 2016, reports "a case of [Dravet syndrome] with an unusually favorable cognitive and behavioral development with a novel SCN1A frameshift mutation." Exhibit C-11 at 144 (abstract). The child was born with a frameshift mutation. Id. at 144-45. This mutation "lead[s] to early protein truncation." Id. at 146. The authors stated: "Logically, the patient would have the more severe phenotype. However, she has exceptionally favorable intellectual ability." Id.

Jiang et al. suggested that "other mechanisms may be existed to influence the SCN1A phenotype, such as modifier genes, developmental variability, accumulation of somatic mutation in lifetime and environmental insults can all contribute to the cognitive outcome." Id. at 144 (abstract).

Dr. Raymond's response to Jiang was contained in a single sentence: "I agree the case reported by Jiang et al shares similarities with [A.V.] which raises the question of a degree of potential somatic mosaicism in both children." Exhibit C at 5.

Assessing the value of evidence concerning loss of function is difficult. Dr. Raymond might be able to infer that from the limited information available that the

child has mosaicism. Alternatively, Dr. Raymond's supposition could be rejected as speculation in that the Jiang authors present no information about mosaicism in their subject.

In oral argument, the Secretary emphasized that the location of the protein that the gene encodes supports a finding that the SCN1A in a mutation caused A.V's outcome. Oral Arg. Tr. at 28. In connection with this argument, the Secretary cited two articles, Claes and Mulley, for the proposition that mutations corresponding to the S4-S6 region of the sodium channel "lead to the more severe phenotypes." Oral Arg. Tr. at 28.

As to the importance of the protein's location, the Secretary's disclosure could have been more explicit. Dr. Raymond's first report states: "Mutations that … affect the primary function of the channel such as the pore region have been demonstrated to have a more severe disease or phenotype associated with them." Exhibit A at 3, citing Guilia Bechi et al. (Exhibit A-8). He did not cite either Claes or Mulley for this proposition. Furthermore, the Secretary did not press an argument about the location or the pore region. Neither "location" nor "pore" appear in his brief.

More problematically, whether A.V's mutation, which is in exon 6, aligns to the S4-S6 region is not clear. The GeneDx report places the mutation in exon 6. Exhibit 4 at 3. However, the SCN1A gene has 26 exons. Exhibit A-7 at 536 (Mulley). Dr. Raymond's reports do not assert that exon 6 corresponds to S4-S6 region of the sodium channel. See Exhibits A, C, D. Without this evidence, a step in the Secretary's argument is missing.

In sum, the evidence regarding the nature of the genetic mutation might tip slightly in the Secretary's favor. One aspect of the A.V.'s genetic mutation supports the Secretary's position: A.V.'s mutation arose de novo and the parties agreed that de novo mutations are more likely to be associated with worse clinical manifestations. However, the significance of two other attributes is less clear. A.V. has a genetic mutation that prevents the creation of the expected protein in its entirety. The location of A.V.'s genetic mutation should, according to respondent's argument, lead to a severe phenotype. But, A.V.'s functioning is relatively good. In other words, she is better than anticipated. The Secretary has

not explained persuasively how A.V. can have developed as well as she has while having the genetic mutation.[25] See Oral Arg. Tr. at 50-51.

D. Human Studies

Through their experts, the parties advance many studies on children with SCN1A mutations. Some of those investigated whether a vaccine affected the outcome.

1. McIntosh

The earliest study and the one that received the most attention is by McIntosh. Special masters have cited McIntosh. See Snyder, No. 7-59V, 2011 WL 3022544 at *23 (Fed. Cl. Spec. Mstr. May 27, 2011) (finding McIntosh confirms Dr. Raymond's opinion); see also Deribeaux, No. 05-306V, 2011 WL 6935504 at *45; Faoro, No. 10-704V, 2016 WL 675491 at *16 (Fed. Cl. Spec. Mstr. Jan. 29, 2016) (relying upon McIntosh and other articles to find respondent established an SCN1A mutation was the sole cause of a child's Dravet syndrome); Oliver, No. 10-394V, 2017 WL 747846 at *16 (finding the "existing medical literature has established that vaccination does not affect the clinical course or prognosis of Dravet syndrome"). Dr. Raymond relied upon McIntosh in his first report. Exhibit A at 6.

The reliance on McIntosh drew a triple response from Dr. Kinsbourne, Dr. Boles, and Dr. McNulty. First, Dr. Kinsbourne asserted that vaccines triggered an earlier onset of seizures in children with Dravet syndrome. Exhibit 45 at 8. Relying upon a study by Yuval Shafrir, Dr. Kinsbourne extended this claim by stating "the earlier onset was associated with the more severe outcome." Id. at 9.

Second, like Dr. Kinsbourne, Dr. Boles maintains: "Vaccination in children with an SCN1A mutation is associated with earlier onset of seizure, generally on the same or the next day." Exhibit 82 at 9. Dr. Boles next uses data from McIntosh to propose that McIntosh was unlikely to detect "poor long-term developmental prognosis." Id. at 12.

Dr. Boles's use of statistics is expanded on by the petitioners' third expert to discuss McIntosh, Mark S. McNulty, PhD. Unlike other experts, who are medical

[25] Mr. and Ms. Vinesar also failed to present a persuasive account for A.V.'s relatively good development. The thrust of their claim is that the vaccine caused A.V. to be worse than she would have been but for the vaccination. Yet, A.V. fortunately does not seem severely injured.

doctors, Mr. McNulty earned a PhD in economics and statistics. Exhibit 81 at 6 (curriculum vitae). Mr. McNulty questions what inferences can be drawn from the data McIntosh presents:

> The direct interpretation is that there is no evidence in this data that DTP vaccinations do impact outcomes, as McIntosh states. However, there is also no evidence that DTP vaccinations do not impact outcomes, and this is the conclusion that McIntosh implicitly makes. McIntosh ignores the fundamental premise of statistical hypothesis testing that failing to reject the null hypothesis does not imply that the null is true.

Exhibit 81 at 2-3. Dr. Raymond agrees. Exhibit C at 10.

One of Mr. McNulty's conclusions is that the "information in the [McIntosh] study data is very limited because of the small sample sizes." Exhibit 81 at 5.

2. Human Studies Other than McIntosh

Dr. Raymond adds other human studies in which the populations were larger. Exhibit C at 12-13, citing Tro-Baumann, Spiczak, Verbeek. Among studies involving human children, Dr. Kinsbourne appears to favor a study by V. Cetica. Exhibit 2 at 1, Exhibit 45 at 9-10.[26]

a) Tro-Baumann

The Tro-Baumann authors retrospectively examined the occurrence of vaccination-related seizures in 70 children with Dravet syndrome with known SCN1A mutations. Exhibit C-30 at 176-77 (Tro-Baumann). All participants received at least one routine vaccination. These vaccines were DTP (diphtheria, tetanus, pertussis), MMR (measles, mumps, rubella), influenza, and pneumococcal vaccine. Id. The results were as follows:

> In total, 34 seizures following vaccination were reported in 19 (27%) of 70 patients at a median age of 6 months (range 3 months to 4.5 years). In 11 (16%) of 70 patients, that is, 58% of all patients with seizures following vaccination, the vaccination-related seizure was the first manifestation of

[26] Dr. Kinsbourne also emphasized two studies involving animal models. Dutton and Salgueiro-Pereira are discussed above.

> Dravet syndrome, with a median interval between vaccination and seizure of 24 h. Twenty-three (68%) of 34 seizures were accompanied by fever, occurring in 10 of 19 patients.

Id.

The authors cited to the McIntosh article, stating that in one patient, "antipyretics were systematically administered before and after all follow-up vaccinations without further vaccination-related seizures." Id. Although McIntosh presents this single case, this example may indicate that vaccination-related seizures might be preventable at least in patients with febrile episodes. Id.

The researchers' "findings highlight seizures after vaccinations as a common feature in Dravet syndrome and emphasize the need for preventive measures for seizures triggered by vaccination or fever in these children." Id. at 175. The authors did not explicitly state whether the vaccinations caused or altered the onset or subsequent course of seizures.

Neither Dr. Kinsbourne nor Dr. Boles opined on Tro-Baumann's article.

b) Brunklaus

Three articles by Brunklaus appear in the record. They are presented in chronological order, starting with the earliest.

(1) Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome (Exhibit 51 and Exhibit C-25)

In 2012, Brunklaus et al. conducted an ordinal logistic regression analysis on 355 patients with Dravet syndrome in order to identify predictors of developmental outcome. Exhibit 51 and Exhibit C-25 at 2331 (Brunklaus). They discovered that the "presence of a motor disorder, abnormal interictal EEG findings in Year 1, status epilepticus and early focal seizures with impairment of awareness (≤ 24 months), were each positively associated with the tendency of a worse developmental outcome." Id. They further noted that "[a] young age at onset of myoclonic seizures and a young age at onset of developmental delay were each associated with the tendency for worse developmental outcome." Id. It does not appear that the authors expressly link this "worse developmental outcome" to the severity of the genetic condition. They also stated that "the different seizure precipitants, photosensitivity, MRI abnormalities or mutation class had no significant effect on developmental outcome." Id.

The authors explained that their analysis of "clinical features reveals an evolution of different seizure types over the first 3 years that corresponds to early descriptions by Charlotte Dravet in 1978." Id. at 2333. The authors found that the "[m]ajority of seizures had been precipitated by fever or illness, however, one-third had no precipitant and 7% had been triggered by vaccination." Id. Pertussis vaccination was once thought to cause vaccine encephalopathy, but "recent evidence demonstrated that the encephalopathy is, in the majority of cases, truly a presentation of Dravet syndrome caused by SCN1A gene mutation (Berkovic et al., 2006)." Brunklaus et al. "found that vaccination-triggered seizures presented significantly earlier than those without precipitant or with fever/illness, nevertheless vaccination itself had no impact on the developmental outcome." Id. at 2334. Based on this finding, the authors commented: "[t]his supports the argument that children carrying a SCN1A mutation are destined to develop the disease, which in turn can be precipitated by a series of factors such as fever/illness, vaccination or a bath." Id. "However, the nature of the trigger has no effect on overall developmental outcome and thus not seem to be responsible for the subsequent encephalopathy." Id.

Brunklaus et al. does not explicitly state that a vaccination-induced initial seizure alters the course of Dravet syndrome. Rather, they explain that it is inevitable that children with a SCN1A mutation will have Dravet syndrome.

> (2) SCN1A variants from bench to bedside improved clinical prediction from functional characterization. (Exhibit C-16)

In October 2019, Brunklaus et al. state that it is difficult to predict disease outcomes based on variant type in the SCN1A gene. Exhibit C-16 at 363 (Brunklaus). Although thousands of SCNIA variants have been reported, "only a minority has been functionally assessed." Id. The authors "review[ed] the functional SCN1A work performed to date, critically appraise[d] electrophysiological measurements, compare[d] this to in silico predictions, and relate[d] [their] findings to the clinical phenotype." Id. Their results revealed that, "regardless of the underlying phenotype, that conventional in silico software correctly predicted benign from pathogenic variants in nearly 90% . . . [but it] was unable to differentiate within the disease spectrum [Dravet syndrome, genetic epilepsy with febrile seizures plus vs. familial hemiplegic migraine]." Id. "In contrast, patch-clamp data from mammalian expression systems revealed functional differences among missense variants allowing discrimination between disease severities." Id. "Those presenting with milder phenotypes retained a degree of channel function measured as residual whole-cell current, whereas those

without any whole-cell current were often associated with [Dravet syndrome]." Id. Based on these findings, the authors concluded that "electrophysiological data from mammalian expression systems can serve as useful disease biomarker when evaluating SCN1A variants, particularly in view of new and emerging treatment options in [Dravet syndrome]." Id.

This article did not discuss whether a vaccination-induced initial seizure alters the course of Dravet syndrome.

(3) Biological concepts in human sodium channel epilepsies and their relevance in clinical practice. (Exhibit C-29)

In January 2020, Brunklaus et al. discussed a study where out of 504 patients with SCN1A variants, 490 had Dravet syndrome and 14 had "generalized epilepsy with febrile seizure plus." Exhibit C-29 at 390 (Brunklaus). "Nearly all [protein-truncating variant] carriers (99.6%) had [Dravet syndrome]." Id. "The authors discussed that "[t]he majority of SCN1A-related epilepsies are caused by [loss of function] missense variants, full gene deletions, and [protein-truncating variants]." Id. at 392.

The authors found that SCN1A steadily increases throughout childhood into adulthood. Id. at 396. "SCN1A is predominantly expressed in inhibitory neurons." Id. The authors explained that "induced pluripotent stem cell work has shown that increased excitability of principal neurons equally contributes to network hyperexcitability in [Dravet syndrome] [and] [t]he distinct developmental and neuronal type-specific expression of SCN1A may explain the phenotypic differences and variations in drug response with exacerbation of seizures in [Dravet syndrome] patients due to [sodium channel blocker] therapy." Id.

This article did not discuss vaccinations.

(4) Parties' Comments on Brunklaus articles

Petitioners did not discuss the Brunklaus articles in their briefs. Petitioners' expert, Dr. Kinsbourne, cited to Brunklaus' *Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome* to demonstrate that the worst developmental outcomes are not associated with the earliest seizure onset. Exhibit 45 at 10. Age at which the first seizure occurred was a more accurate factor in predicting the severity of subsequent developmental delay. Id.

Respondent referred to all three Brunklaus articles and concluded that they do not show a vaccination-induced initial seizure alters the course of Dravet syndrome. Resp't's Br. at 28, 34.

c) Verbeek

Verbeek wrote three articles, discussing the role of vaccination, febrile seizures, and Dravet syndrome, contained in the record.

(1) Prevalence of SCN1A-Related Dravet Syndrome among Children Reported with Seizures following Vaccination: A Population-Based Ten-Year Cohort Study (Exhibit C-32)

Verbeek et al. conducted a study "to determine the prevalence of Dravet syndrome, an epileptic encephalopathy caused by SCN1A-mutations, often with seizure onset after vaccination, among infants reported with seizures following vaccination . . . [and] differences in characteristics of reported seizures after vaccination in children with and without SCN1A-related Dravet syndrome." Exhibit C-32 at 1[27] (Verbeek). In the study, the researchers identified: "*SCN1A*-related Dravet syndrome [was] the underlying cause in 1.2% of children reported with seizures following vaccinations in the first two years of life, including 2.5% of seizures reported after vaccination in the first year of life, and 0.3% in the second year of life. Among seizures reported after the second or third DTP-IPV(-)Hib vaccination, the proportion of *SCN1A*-related Dravet syndrome was the highest." Id. at 6. The authors reported: "The seizure had occurred within 24 h (median 7.5 h) after administration of DT(P)-IPV(-)Hib vaccines in the majority of children diagnosed with *SCN1A*-related Dravet syndrome. Children diagnosed with *SCN1A*-related Dravet syndrome had a younger age at first seizure following vaccination, and more often had second and third seizures reported after subsequent vaccinations than other children. Both short or prolonged, generalized or unilateral, and febrile or afebrile vaccination-related seizures occurred in children with *SCN1A*-related Dravet syndrome. Seizures occurred more often with a body temperature below 38.5°C, illustrating the high sensitivity also to minor temperature increase in children with *SCN1A*-related Dravet syndrome." Id. The authors concluded:

[27] The Secretary submitted this article in manuscript form. Therefore, the page cites in Exhibit C-32 are to the pdf version, rather than the version that appears in printed journals.

> In children with Dravet syndrome, vaccinations might induce the first and following seizures. Physicians and co-workers of immunization safety surveillance should have knowledge of the prevalence of Dravet syndrome among children reported with seizures following vaccinations, and of the discriminating seizure characteristics in this subgroup. This will promote earlier diagnoses of Dravet syndrome which is appropriate treatment and genetic counseling. *Moreover, an early diagnosis will prevent parents and professionals from assuming that vaccination is the cause of the epilepsy, and will thereby promote faith and participation in immunization programs*.

Id. at 8 (emphasis added).

(2) Etiologies for Seizures Around the Time of Vaccination (Exhibit C-33)

Verbeek et al. assessed "the incidence, course, and etiology of epilepsy with vaccination-related seizure onset in a population-based cohort of children." Exhibit C-33 at 658 (Verbeek). In a study of 23 children with epilepsy onset after vaccination, 12 of them developed epileptic encephalopathy, 8 had benign epilepsy, and 3 had encephalopathy before seizure onset. Id. The authors identified underlying causes in 15 children (65%), which included SCN1A-related Dravet syndrome or genetic epilepsy with febrile seizures plus syndrome, a protocadherin 19 mutation, a 1qter microdeletion, neuronal migration disorders, and other monogenic familial epilepsy. Id. The authors reasoned that the "administered vaccines could have acted as a trigger for the first seizure, thereby *unmasking the genetic seizure predisposition in the children* [in their cohort study]." Id. at 663 (emphasis added). The authors stated that "[s]eizure precipitation by vaccination or fever is a hallmark of SCN1A-related Dravet syndrome." Id. These findings led the authors to conclude that "in most cases, genetic or structural defects are the underlying cause of epilepsy with onset after vaccination, including both cases with preexistent encephalopathy or benign epilepsy with good outcome." Id.

(3) Effect of vaccinations on seizure risk and disease course in Dravet syndrome (Exhibit 78 and Exhibit C-34)

Verbeek et al. studied "the effect of vaccination-associated seizure onset on disease course and estimate[d] the risk of subsequent seizures after infant pertussis combination and measles, mumps, and rubella (MMR) vaccinations in Dravet

syndrome." Exhibit C-34 at 596 (Verbeek).[28] In a study, "[c]hildren who had [Dravet syndrome] with and without vaccination-associated seizure onset (21% and 79%, respectively) differed in age at first seizure (median 3.7 vs 6.1 months) but not in age at first nonvaccination-associated seizure, age at first report of developmental delay, or cognitive outcome." Id. The authors found: "The risk of subsequent vaccination-associated seizures was significantly lower for acellular pertussis (9%) and nonpertussis (8%) than whole-cell pertussis (37%) vaccines. Self-controlled case series analysis showed an increased incidence rate ratio of seizures of 2.3 (95%) within the risk period of 5 to 12 days following MMR vaccination." Id. These findings "suggest that vaccination-associated earlier seizure onset does not alter disease course in [Dravet syndrome], while the risk of subsequent vaccination-associated seizures is probably vaccine-specific." Id.

(4) Parties' Comments on Verbeek Articles

While petitioners did not cite to Verbeek in the briefs, Dr. Boles cited to Verbeek, stating that "35% of the cases having SCN1A-related [Dravet syndrome] does suggest that this gene is an important part of the vaccine-associated epilepsy population." Exhibit 82 at 9. Dr. Kinsbourne also stated Verbeek and colleagues "misinterpreted negative statistical outcomes as flagrantly as did McIntosh and colleagues." Exhibit 45 at 9; accord Exhibit 109 at 9.

Respondent and Dr. Raymond cited to all three Verbeek articles, concluding that they do not show a vaccination-induced initial seizure alters the course of Dravet syndrome. Resp't's Br. at 36; Exhibit C at 12-13.

d) Spiczak

Spiczak et al. recognized that "little is known about the type and frequency of seizures and epilepsy syndromes following vaccination" and strove to understand it better by conducting a study with a goal "to describe the clinical features of children presenting with seizures after vaccination using a register-based cohort." Exhibit C-31 at 1506 (Spiczak). In a study of 247 patients with seizures of epilepsy, the authors found that severe childhood epilepsies (Dravet syndrome, West syndrome, Lenox-Gastaut syndrome, or Doose syndrome) were diagnosed in 29 (11.7%) of those 247 patients, with the vaccination-associated event being the first documented seizure in 15 (51.7%) of 29 patients. Id. Clinical

[28] Although Exhibit 78 and Exhibit C-34 are the same article, only Exhibit C-34 is cited to because it is the entire article.

history was strongly suggestive of Dravet syndrome in 8 (3.2%) of 247 cases. Of these, *SCN1A* mutations were reported in four cases (1.6%, referred to as "confirmed Dravet syndrome"). Results of the *SCN1A* mutation analysis were not available in 3 of 8 cases and were negative in 1 of 8 cases (all referred to as "suspected Dravet syndrome"). Id. at 1509.

> Because the clinical information provided was strongly suggestive of Dravet syndrome in . . . 1.6% [cases] and genetic factors are increasingly identified in patients with West syndrome (Watanabe, 1998), [Spiczak et al.] suggest that causal genetic factors could potentially be identified in a sizeable subset of patients with severe childhood epilepsies and vaccination-associated seizures, helping to further demystify the concept of "vaccine encephalopathy.

Id. at 1510.

Spiczak et al. explained that "[i]n a recent study, the majority of cases of alleged 'vaccine encephalopathy' had Dravet syndrome following reevaluation (severe myoclonic epilepsy of infancy; Dravet et al., 2005) and mutations in *SCN1A,* encoding the alpha-1 subunit of the sodium channel (Claes et al., 2001; Suls et al., 2006; Harkin et al., 2007), were identified in 11 of 14 patients (Berkovic et al., 2006), *showing that genetic epilepsy syndromes might masquerade as vaccination-related epilepsies*." Id. at 1507 (emphasis added).

Spiczak et al. concluded that "[v]accination-associated seizures present in the setting of various epilepsy syndromes, including severe childhood epilepsies in >10% of cases [and] [e]arly diagnosis of the corresponding epilepsy syndromes and confirmation of an underlying etiology is important for treatment decisions, genetic counseling, and public health evaluation of vaccine safety." Id. at 1506.

Dr. Raymond discussed the Spiczak article, but Dr. Kinsbourne and Dr. Boles did not.

e) Cetica

Cetica et al. retrospectively "studied 200 individuals with SCN1A mutations and explored the prognostic value of mutational data and early clinical findings that may help clinicians to set up management choices adapted to individuals at higher risk of progressing to Dravet syndrome, without delaying them until the epileptic encephalopathy has become obvious." Exhibit C-37 at 1038 (Cetica). They found: "Age at seizure onset, analyzed as both a continuous and a categorical variable, was distributed differently in patients with Dravet and those without

Dravet syndrome. Mean age at first seizure was 5.19 months for patients with Dravet and 18.4 months for those without Dravet syndrome . . . . None of the patients who experienced their first seizure after 12 months of age developed Dravet syndrome." Id. at 1040. This study led the authors to conclude that age at seizure onset appears to be a reliable indicator of outcome. Id. at 1043. They recommended "early recognition and treatment that mitigates prolonged/repeated seizures in the first year of life," limiting the progression to epileptic encephalopathy, because outcome is not predetermined by genetic factors only. Id. at 1037.

While Dr. Kinsbourne cited to the Cetica article for support, petitioners did not mention any argument based upon this article in their briefs. Exhibit 2 at 1, Exhibit 45 at 9-10.

Dr. Raymond and respondent, however, address the Cetica study. Exhibit A at 5, Exhibit C at 14, Resp't's Br. at 35. Dr. Raymond discussed that a subsequent review in 2019 by the same individuals as Cetica et al. "recognize[d] the major significant finding of their paper in finding the ability to predict the significance of a mutation was whether it resulted in earlier onset of seizures or not." Exhibit C at 14. Dr. Raymond stated the authors did not "appear to be endorsing that their review demonstrates any role of early seizure in a change of outcome." Id.

In this 2019 study by the Cetica group, the researchers stated that "[i]t has now been clarified that the clinical spectrum of the [Dravet] syndrome does not have firmly established boundaries." Exhibit C-38 at S2 (Mei). They explained that "[c]ognitive impairment is invariably present when the full syndrome is manifested . . . [amd] [t]his complex of symptoms is related to mutations in the SCN1A gene . . ." Id. They stated: "Inheritance from less severely affected individuals, at times only having experienced a few febrile seizures, and differences in severity, even within the same family, with a subset of patients only showing fragments of the syndrome, testify to a remarkable phenotypic heterogeneity as far as severity, but less so clinical phenomenology, are concerned." Id. They opined that the SCN1A gene-Dravet syndrome association is "highly specific" and reasoned that "because the syndrome spectrum is wide, fragments of it can at times also be manifested in other genetic epilepsy syndromes, thereby leading to overdiagnosis of Dravet syndrome beyond SCN1A." Id. They concluded that "Dravet syndrome is in turn a severe SCN1A phenotype within a continuum of SCN1A-related clinical phenomenology." Id.

3. Synopsis

Overall, this category of evidence (studies involving human children) favors the Secretary's position. It must be recognized that these studies are not perfect. For example, the researchers did not withhold a vaccine from children with a mutation to see whether they developed seizures in the absence of vaccination. The creation of this type of control group would raise ethical questions. The studies also do not include thousands of subjects. See Exhibit C at 11 (Dr. Raymond's discussion of the challenges of studying rare disorders). However, a perfect study is not a requirement. See Sullivan v. Sec'y of Health & Hum. Servs., No. 10-398V, 2015 WL 1404957, at *20 (Fed. Cl. Spec. Mstr. Feb. 13, 2015) (discussing that "the possibility of a *better* study is not an effective critique of an existing, otherwise valid study"); see also Harris v. Sec'y of Health & Hum. Servs., No. 10-322V, 2014 WL 3159377, at *13 (Fed. Cl. Spec. Mstr. June 10, 2014) (stating that the "perfect scientific study is not required by the relevant legal standards"), but see Sanchez, 34 F.4th 1350, 1356 ("a single example does not establish the typical progression of a disease and is not 'sufficient to disprove a medical theory that a vaccine *can* cause aggravation in *some* patients'").

Multiple groups have explored whether childhood vaccines cause or worsen seizures in children with SCN1A mutations. Using different approaches, investigators have not detected any evidence that vaccines alter the child's seizure pattern. Instead, the large studies tend to show that the genetic mutation causes the seizures.

E. Previous Cases

The foregoing four sections (parts VI.A through VI.D) of analysis largely matches the findings by special masters in other cases involving a SCN1A mutation. See Stone, 2010 WL 1848220, at *42; see also Hammitt, 2010 WL 3735705, at *47; Deribeaux, 2011 WL 6935504, at *46, Harris, 2011 WL 2446321, at *35. In two precedential opinions and one non-precedential opinion, the Federal Circuit ruled that the finding of a genetic mutation was the sole cause of a child's epilepsy was not arbitrary. Stone, 676 F.3d at 1381-86, Deribeaux, 717 F.3d at 1369, Snyder, 553 Fed. App'x at 1002-04. The panels from the Federal Circuit acknowledged the deferential standard of review for findings of fact.

In the decisions underlying those Federal Circuit opinions, special masters considered multiple factors:

- Details about what is known about the nature of the mutation, such as arising de novo and occurring in a well conserved region. Stone, No. 04-1041V, 2010 WL 1848220, at *19; Harris, 2011 WL 2446321, at *15-16

- The mutation's effect on the resulting structure of the sodium channel. Deribeaux, 2011 WL 693-5504, at *35-36, 40-41

- Dr. Raymond's expertise in genetics. Stone, 2010 WL 1848220, at *40; Harris, 2011 WL 2446321, at *6.

The special masters also:

- Determined a showing of a specific genotype – phenotype combination was not required. Stone, 99 Fed. Cl. at 190; Deribeaux, 2011 WL 6935504, at *42, mot. for review denied on this point, 105 Fed. Cl. at 596; but see Harris, 102 Fed. Cl. at 302 (2011) ("a one-to-one relationship has not been established"), rev'd sub nom. Snyder, 553 F. App'x 994 (Fed. Cir. 2014).

- Concluded that definitive proof of mutations' causative effect was not required. Deribeaux, 2011 WL 6935504, at *32.

- Rejected a theory that the genetic mutation only created a predisposition or vulnerability to developing epilepsy. Hammitt, 2010 WL 3735705, at *10 (Dr. Kinsbourne); Deribeaux, 2011 WL 6935504, at *27 (Dr. Tornatore).

These cases were a foundation for the special master's decision in Oliver, No. 10-394V, 2017 WL 747846. There, the petitioners advanced the theory that the genetic mutation created susceptibility to a further injury. Id. However, the special master rejected that theory and found the genetic mutation caused the child's epilepsy.

A majority of the Federal Circuit panel ruled that the special master's finding was not arbitrary. Accordingly, the panel affirmed the judgment, denying compensation. Oliver, 900 F.3d at 1361–62.

When the petitioners/appellants in Oliver requested *en banc* review, the Federal Circuit denied the petition. But, a dissent from a denial of the rehearing *en*

banc maintained that Snyder, Deribeaux, and Stone were flawed and should be overruled. Oliver, 911 F.3d at 1385-86 (Newman, J., dissenting).

In short, before 2018, the Federal Circuit had ruled in four opinions (reflecting six cases) in which a child-vaccinee possessed an SCN1A mutation that a special master could reasonably find the mutation was the sole cause of the child's epilepsy. But, in the Vinesars' view, Sharpe changes everything. See Pet'rs' Br. at 10-11, Pet'rs' Reply at 3-4.

From one perspective, the Vinesars' argument matches what the Federal Circuit did and said. The Federal Circuit stated that a "deterministic mindset does not belong in the Vaccine Injury Program." 964 F.3d at 1084. For this proposition, the Federal Circuit cited the dissent in Oliver's denial of a rehearing *en banc*. The Federal Circuit in Sharpe did not reconcile its rejection of genetic determinism with its earlier acceptance of findings from special masters in Stone, Deribeaux, Harris, and Oliver.

One way that Sharpe differs from Stone etc. is that the genetic mutation in Sharpe was a mutation in the DYNC gene. Sharpe, 2018 WL 7625360, at *3. In Stone, Deribeaux, Harris, and Oliver, the genetic mutation was in the SCN1A gene.

Another potential distinction between Sharpe and Stone etc. could be that the opinions from the government's experts differed. In the SCN1A cases, the government's expert, Dr. Raymond, opined the genetic mutation was the sole reason for the child's epilepsy. In contrast, in Sharpe, the government's expert, Dr. Descartes, was more equivocal. The Federal Circuit quoted this aspect of her testimony:

> The dream of the geneticist is to find genotype-phenotype correlation, because when a parent comes to talk to me, the first thing they want to know, is my child going to be able to do this and that? How long my child is going to live? Do you have any answer to these questions? The mutation that you found, what do you know? And the answer, unfortunately, to all these questions that parents ask all the time is **we don't know.**

964 F.3d at 1082 (emphasis supplied by the Federal Circuit).

This equivocation from the Secretary's expert is not present in the Vinesars' case. Dr. Raymond has consistently explained that the SCN1A mutation is the cause for A.V.'s seizure disorder. Exhibit A at 6; Exhibit D at 3.

The potential distinction between the evidence as a basis to harmonize, on the one hand, Stone, Deribeaux, Snyder, and Oliver with, on the other hand, Sharpe is less apparent with respect to Sanchez. In Sanchez, Dr. Raymond opined "Trystan's genetic mutations, and solely his genetic mutations, caused Trystan's Leigh's syndrome." Sanchez, No. 11-685V, 2020 WL 5641872, at *59. This testimony contributed to approximately ten pages of analysis following the methodology the Federal Circuit appeared to endorse in Stone. Sanchez, 2020 WL 5641872, at *60. Nevertheless, the Federal Circuit determined "There is no evidence … that Trystan's mutations would have resulted in the same progression and severity of his Leigh's syndrome absent the vaccine." Sanchez, 34 F.4th at 1356.

The result in Sanchez is, the undersigned respectfully submits, difficult to understand. Can Dr. Raymond's opinion satisfy the preponderance of the evidence standard? What is the minimum quantity and quality of evidence required for the Secretary to prevail on an alternative factor defense? Is the Secretary required to present a study involving people with the genetic mutation who did and did not receive a vaccine? In this respect, the Federal Circuit in Sanchez criticized the (undersigned) special master for relying in part upon a gene expression study in which researchers determined a relevant genetic mutation would cause a disease. However, this level of proof was not available in Stone and Deribeaux.[29] Understanding the view of the Federal Circuit would help this special master comply with the instructions and expectations of the controlling Circuit Court.

To the extent that the two more recent precedential opinions (Sharpe and Sanchez) cannot be reconciled with the three earlier precedential opinions (Stone, Deribeaux and Oliver), the earlier panel controls. Robert Bosch, LLC v. Pylon Mfg. Corp., 719 F.3d 1305, 1316 (Fed. Cir. 2013) (*en banc*); Johnston v. IVAC Corp., 885 F.2d 1574, 1579 (Fed. Cir. 1989). Thus, a finding that an SCN1A mutation was the sole cause of an epilepsy would seem consistent with the outcomes in Stone, Deribeaux, and Oliver and would seemingly not necessarily violate any dictates set out in Sharpe and Sanchez.

[29] Although the Federal Circuit affirmed the judgments denying compensation, the Federal Circuit did not comment on whether a specific genotype-phenotype precedent was required.

The Federal Circuit's rulings that a special master was not capricious do not preclude a different outcome. See Lampe v. Sec'y of Health & Hum. Servs., 219 F.3d 1357, 1368 (Fed. Cir. 2000); Bean-Sasser v. Sec'y of Health & Hum. Servs., 127 Fed. Cl. 161, 167 (2016); [M.S.B.] by Bast v. Sec'y of Health & Hum. Servs., 117 Fed. Cl.104, 124 (2014) (discussing opinions from the Court of Federal Claims). Outcomes could differ because the underlying evidence is different. However, the outcome in the Vinesars' case resembles the evidence in those other cases. For example, Dr. Raymond has testified in all the SCN1A cases. This evidence, which has been discussed at length above, still preponderates in favor of finding that the SCN1A mutation, by itself, causes a child's epilepsy.

After scientists discovered an association between SCN1A mutations and Dravet's syndrome, scientists have, in many contexts, determined that the mutation caused the seizure disorder. For example, in 2012, Brunklaus and others concluded: "children carrying a SCN1A mutation are destined to develop the disease." Mr. and Ms. Vinesar have not presented persuasive evidence to contradict the scientific conclusion reached by multiple sets of researchers.

F. Summary regarding Factor Unrelated

If the Secretary bore a burden to demonstrate that a factor unrelated to the vaccination caused A.V.'s seizure disorder, the Secretary met that burden. With preponderant evidence, the Secretary demonstrated that the A.V.'s genetic mutation was the sole cause of her seizure disorder. This evidence primarily consists of experiments on animals that model SCN1A mutations, information about the details of A.V.'s specific mutation, and results of multiple studies about children with SCN1A mutations published in peer-reviewed journals. Dr. Raymond, who has more experience treating children and their families for genetic-based neurologic problems than either Dr. Kinsbourne or Dr. Boles, persuasively supported his opinion that a mutation in A.V.'s SCN1A gene "is the sole cause of her epilepsy." Exhibit D at 3.

Furthermore, the result in A.V.'s case (a finding that a genetic mutation caused a seizure disorder) is the result reached in all other cases involving an SCN1A mutation. While those results do not dictate the outcome here, they do provide some persuasive precedent.

VII. A Hearing Is Not Required

Special masters possess discretion to decide whether an evidentiary hearing will be held. 42 U.S.C. § 300aa-12(d)(3)(B)(v) (promulgated as Vaccine Rule 8(c)

& (d)). A special master may decline to conduct a hearing when each party has enjoyed a full and fair opportunity to present its position. Kreizenbeck v. Sec'y of Health & Hum. Servs., 945 F.3d 1362, 1366 (Fed. Cir. 2020); Bello v. Sec'y of Health & Hum. Servs., 158 Fed. Cl. 734, 748-49 (2022). A key question is whether the special master has considered all the relevant evidence. Mager v. Sec'y of Health & Hum. Servs., 158 Fed. Cl. 136, 149 (2022). Here, two considerations lead to the conclusion that a hearing is not required.

First, the parties (particularly the Vinesars) have had ample opportunity to submit evidence supporting their position. The Vinesars have submitted more than a half-dozen reports, from a total of three experts. Exhibits 2, 45, 46, 81, 82, 109, 114, 153. These reports allowed Dr. Kinsbourne, Dr. Boles, and Dr. McNulty a chance to respond to opinions Dr. Raymond had expressed. After the submission of expert reports concluded, the Vinesars were given an opportunity to submit a comprehensive brief but declined. See Orders, issued Jan. 13, 2022 (proposing topics for a brief) and Jan. 27, 2027 (reporting comments from a status conference). To the extent that the Vinesars proposed a hearing to address topics that they had not previously addressed, see Oral Arg. Tr. at 37, those requests are too late. The proper time to disclose an expert's opinion is in the written report. Simanksi v. Sec'y of Health & Human Servs., 671 F.3d 1368, 1382 (Fed. Cir. 2012) (stating "the special master can order the experts to confine their testimony to the issues addressed in their reports"). Accordingly, the Vinesars have had a fair and full opportunity to present evidence.

Second, from the Vinesars' perspective, they do not need any additional evidence. The Vinesars stated that the matter could be resolved on the papers "as no material fact is in dispute." Pet'rs' Br. at 1. The essence of their claim is that (1) an SCN1A mutation creates a propensity (or predisposition or vulnerability) to developing seizures, and (2) a vaccine can induce a fever and a fever can trigger the propensity for a seizure.

For their argument that the SCN1A mutation predisposes a person to having seizures (as opposed to causing the seizures), the Vinesars largely emphasize the Federal Circuit's opinion in Sharpe. (As noted earlier, the Federal Circuit's opinion in Sanchez, arguably, helps them even more than Sharpe does.) If an appellate authority were to determine that the Sharpe and Sanchez approach to analyzing cases with genetic mutations were the correct approach, then the Vinesars could prevail on the component regarding petitioners' burden to explain how a vaccine can cause a previously unmanifest condition to become manifest and/or petitioners' burden to explain how a vaccine can significantly aggravate a clinically silent genetic condition. On the other hand, if an appellate authority

were to determine that the Stone, Deribeaux, and Oliver approach were correct, then the Vinesars could not prevail.

VIII. Conclusion

As with other parents whose children have genetic mutations and seizure disorders, the Vinesars have endured and are enduring complicated and challenging medical situations. They merit sympathy for everything they and their beloved daughter have suffered.

However, sympathy is not the standard for awarding compensation. For the reasons explained above, they have not demonstrated that the vaccination caused any lasting harm in A.V. In addition, the Secretary has demonstrated with preponderant evidence that the SCN1A mutation is the sole cause of her seizure disorder. Accordingly, the Vinesars are not entitled to compensation.

The Clerk's Office is instructed to issue judgment in accord with this decision unless a motion for review is filed. Information about filing a motion for review, including the deadline, is found within the Vaccine Rules, which are available on the website for the Court of Federal Claims.

IT IS SO ORDERED.

s/Christian J. Moran
Christian J. Moran
Special Master